Title
General Approach to the Synthesis of the Chlorosulfolipids Danicalipin A, Mytilipin A, and Malhamensilipin A in Enantioenriched Form and Progress towards the Synthesis of the Psammaplysin Family of Natural Products

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IRVINE

General Approach to the Synthesis of the Chlorosulfolipids Danicalipin A, Mytilipin A, and Malhamensilipin A in Enantioenriched Form

and

Progress towards the Synthesis of the Psammaplysin Family of Natural Products

DISSERTATION

submitted in partial satisfaction of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Joseph Scott Carlson

Dissertation Committee:
Professor Christopher D. Vanderwal, Chair
Professor Larry E. Overman
Professor Zhibin Guan

2015
DEDICATED TO

Nora Jean Love
1922–2012
Beloved grandmother,
and the kindest person I’ve ever known

and

Julie and Bill Carlson
for their unconditional love and support

There is no disgrace in not knowing,
but there is in not wanting to learn.
-Socrates
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CURRICULUM VITAE

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Research Experience

Graduate Student Researcher, UC Irvine, Prof. Chris D. Vanderwal Lab (Sept 2010 – May 2015)
- Unified synthetic strategy of the chlorosulfolipid family of natural products
- Studies towards a divergent synthesis of spirocyclic bioactive natural products

Medicinal Chemistry Intern, Gilead Sciences (July – Sept 2009)
- Synthesized novel drug targets for the treatment of hepatitis C
- Generated library of potent inhibitors of HCV NS5B

Summer Undergraduate Research Fellow, UC Santa Cruz, Prof. Joseph P. Konopelski Lab (July – Sept 2008)
- Assisted in optimization of key steps toward the synthesis of the Psymberin pyran core
- Developed resolution conditions to access a key enantioenriched intermediate

Undergraduate Researcher, Cal Poly State University, Prof. Philip Costanzo Lab (Sept 2008 – June 2010)
- Synthesis of RAFT initiator and triblock copolymers
- Developed novel polymer coupling via thiazolidine linkage

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University of California, Irvine
Ph.D. in Organic Chemistry (2015)
- National Science Foundation Graduate Research Fellowship (2011 – 2014)

California Polytechnic State University, San Luis Obispo
B.S. in Chemistry (ACS Certified) (2010)
- Undergraduate Researcher of the Year (2010)

Publications


ABSTRACT OF THE DISSERTATION

General Approach to the Synthesis of the Chlorosulfolipids Danicalipin A, Mytilipin A, and Malhamensilipin A in Enantioenriched Form

and

Progress towards the Synthesis of the Psammaplysin Family of Natural Products

By

Joseph Scott Carlson

Doctor of Philosophy in Chemistry

University of California, Irvine, 2015

Professor Christopher Derek Vanderwal, Chair

The dissertation describes a second-generation synthesis of three structurally related chlorosulfolipid natural products. Chapter 1 of the dissertation focuses on the discovery and state of the synthetic art of the chlorosulfolipids at the time this work began. Chapter 2 of the dissertation describes the key advances made, include highly stereocontrolled additions to α,β-dichloroaldehydes, kinetic resolutions of complex vinyl epoxide intermediates, and Z-selective cross metatheses of vinyl epoxides.

Chapter 3 of the dissertation describes background information pertaining to the psammaplysin family of natural products, including their biosynthesis and relevant bioactivity. Also described is the retrosynthetic strategy developed for the synthesis of all members of the psammaplysin family of natural products, featuring a donor-acceptor cyclopropane fragmentation as the key step. Chapter 4 details the exploration of several strategies designed to evaluate the best methods for: incorporation of the secondary stereogenic alcohol, donor-acceptor cyclopropane fragmentation/spirocyclic ring formation, and oximinoamide incorporation. A ketene Diels–Alder
disconnection strategy was successful in producing the spirooxepin-isoxazoline ring fusion present in the psammaplysin family of natural products. Also described are preliminary results for incorporation of the stereogenic alcohol at an early stage intermediate that has the potential for being elaborated further using the ketene Diels–Alder strategy.
Chapter 1: Introduction to the Chlorosulfolipid Family of Natural Products

1.1 Introduction

Although they had been reported nearly four decades prior,\(^1\)\(^-\)\(^16\) and despite their interesting biological properties, the chlorosulfolipids (Figure 1.1) received no attention from the synthetic community until recently. It is possible that the task of stereoselectively installing multiple carbon chlorine bonds on a structure that possessed little rigidity seemed like a daunting task. Since 2009 however, the groups of Carreira,\(^17\)\(^-\)\(^20\) Yoshimitsu,\(^21\)\(^-\)\(^23\) Matsuda,\(^24\) and Vanderwal\(^25\)\(^-\)\(^31\) have contributed syntheses of chlorosulfolipids and, in so doing, have taken what once looked like intractable problems for synthesis and found multiple creative ways for their construction. With the exception of Carreira’s tour de force synthesis of the proposed structure\(^11\) of mytilipin B (1.4) that determined the incorrectness of that structure;\(^19\) all of the published work to date has been focused on the three structurally similar chlorosulfolipids danicalipin A (1.1),\(^21\)\(^,\)\(^24\)\(^,\)\(^26\)\(^,\)\(^31\) malhamensilipin A (1.2)\(^28\)\(^,\)\(^31\) and mytilipin A (1.3) (renamed from hexachlorosulfolipid).\(^17\)\(^,\)\(^23\)\(^,\)\(^29\)
1.2 Discovery and Structure Determination

Haines and Block were the first to isolate lipids from the chrysophyte (golden algae) *Ochromonas danica*. The isolation and characterization of 1.6 was achieved by hydrolysis of the sulfates and performing mass spectrometry and derivatization studies on the diol 1.7 (Figure 1.2). A diagnostic mass spectrometric fragmentation pattern $\alpha$ to the alcohol was useful for determining the structure of 1.7. The relative *syn* stereochemistry of 1.7 was determined by characterization of the *cis*-epoxide derivative after treatment with base. The absolute stereochemistry was inferred at the time by comparison of the optical rotations of natural samples to known standards. Elovson and Vagelos have also disclosed the isolation of several lipid diols containing between one and six chlorine atoms as determined by mass spectrometry. These workers went on to correctly determine the planar structure of danicalipin A (1.1) in an incredible degradation and derivatization study. The relative
configuration of danicalipin A was established by Vanderwal and confirmed via synthesis by the Vanderwal group in 2009\textsuperscript{26} and by NMR analysis by the Okino group.\textsuperscript{13}

**Figure 1.2** Structure of simplest chlorosulfolipid isolated from *O. danica*.

Malhamensilipin A (1.2) was isolated in 1994 by the groups of Slate and Gerwick from the algae *Poterioochromonas malhamensis* (renamed from *O. malhamensis*).\textsuperscript{9} The advances in NMR analysis allowed for the determination of the planar structure of 1.2 without the need for extensive degradation or mass spectrometric studies. Although malhamensilipin A bears striking similarity to danicalipin A, there are three distinct differences: (1) The tetracosane lipid backbone (compared to the docosane backbone of danicalipin A); (2) the presence of a chlorovinyl sulfate (presumably derived from the 2,2-dichloro-1-sulfate functionality as is present on danicalipin A); and (3) the varying chlorination pattern at C11, C12 and C16. The structure and absolute configuration of 1.2 was further elucidated by the Vanderwal lab in collaboration with the Gerwick lab via NMR and mass spectrometry methods\textsuperscript{27} and eventually confirmed by chemical synthesis.\textsuperscript{28}

Chlorosulfolipids 1.3-1.5 were isolated between 2001 and 2004 from mussels harvested during periods of algal blooms by the groups of Ciminello and Fattorusso from the digestive glands of mussels deemed toxic.\textsuperscript{10-12} Presumably these chlorosulfolipids are produced by an unidentified alga and then bioaccumulate in the mussels from which they were isolated. Although mytilipin A (1.3) shares many similarities to 1.1 and 1.2, 1.4 and 1.5 are radically different, containing a staggering 11 chlorine atoms, free and sulfated hydroxyls along the lipid backbone in a contiguous and irregular
stereochemical relationship. For the first time the relative configuration of a chlorosulfolipid was
determined using exclusively NMR techniques such as Murata’s method of $J$-based configurational
analysis (JBCA) which relied on the measurements of $^3J_{H,H}$, $^3J_{C,H}$ and $^2J_{C,H}$ coupling constants.$^{32,33}$
The method was originally used to assign the relative stereochemistry of polyketides. The $^3J_{H,H}$ and
$^3J_{C,H}$ coupling constants follow a Karplus curve that relates their magnitude to the dihedral angle.
The $^2J_{C,H}$ coupling constant relates the dihedral angle between the carbon bound electronegative
substituent and the adjacent proton. In combination with nuclear Overhauser effect (nOe) and
rotational Overhauser effect (rOe) analysis Newman projections were constructed and the relative
stereochemistry between adjacent stereocenters in 1.3-1.5 was determined.$^{10-12}$

In 2010 the Carreira group expanded the utility of the $J$-based configurational analysis method to
include the characterization of polychlorinated systems by recalibrating the magnitude of expected
coupling constants. This goal was accomplished by using synthetic samples for which they had
obtained X-ray crystallographic data.$^{18}$

**Figure 1.3** Proposed low-energy solution state conformation for mytilipin A

It is not explicitly stated in the characterization papers by Ciminello and Fattorusso, but the Newman
projections generated using $J$-based configurational analysis also provided important information
about the preferred solution state conformations of 1.3. It can also be inferred that all of the
chlorosulfolipids possess a preferred solution state conformation—one that minimizes all syn-
pentane-like interactions (steric preference) and maximizes the gauche orientation of the vicinal polar groups (stereoelectronic preference) (Figure 1.3).1,34,35

1.3 Biological Relevance and Biosynthesis

There are many interesting facets of the chlorosulfolipid family of natural products that have surprised the scientific community. It was revealed in 1974 that the algae from which danicalipin A (1.1) was isolated contains minimal amounts of phospholipids, which are nearly ubiquitous cell membrane components in most biological systems.36 Instead the researchers found a large amount of N,N,N-trimethylhomoserine, which may serve as a replacement for phospholipids. In subsequent studies, it was shown that danicalipin A (1.1) comprises about 90% of the total polar lipids in the flagellar membrane of Ochromonas danica.37,38 This is surprising considering that the polar sulfate at the middle and terminus of danicalipin A makes it hard to rationalize how it could form a stable lipid bilayer. The ability for danicalipin A to form a hairpin, putting the hydrophobic regions of the molecule away from the polar sulfates, is limited due to the stereoelectronic preference of the chlorine atoms. Nevertheless, the large amount of danicalipin A present in the organism strongly suggests that it plays a structural role in O. danica. In order to rationalize a thermodynamically favorable membrane, Haines has postulated the possibility of another structural component such as a divalent metal atom or coordinating protein to offset the negative charge of the sulfates.37 Further understanding the evolutionary benefit of these unusual lipids to algae is tethered to our understanding of the structural role the chlorosulfolipids play in forming stable lipid bilayers. Towards that goal an efficient synthesis of the chlorosulfolipids appeared necessary to provide authentic samples for in-depth analysis.
It has been shown that Malhamensilipin A (1.2) possess antimicrobial activity and moderate pp60 protein kinase inhibition. Chlorosulfolipids 1.3–1.5 have also been suggested as the causative agents in Diarrhetic Shellfish Poisoning. It is unknown if a specific mode of action exists, or if simply the detergent nature of the ambiphilic compounds causes the observed activity.

The biosynthetic origin of the chlorosulfolipids in the context of O. danica has been investigated by several groups. It was eventually determined through isotope labeling studies that the biosynthesis begins with docosanoic acid (1.8), a product of fatty acid synthesis. The acid is then oxidized at the C14 position using molecular oxygen, followed by reduction of the acid to yield the diol 1.9. Sulfation via enzyme-mediated transfer of the sulfate on 3′-phosphoadenosine-5′-phosphosulfate (PAPS) is proposed to be the final step in the synthesis of 1.10. At this point, a complex matrix-like sequence of free-radical chlorinations likely takes place to produce various chlorinated intermediates such as 1.11 and 1.12 (Scheme 1.1). This has been demonstrated by the fact that radiolabeled chloride intermediates 1.11 and 1.12 can be isolated and resubjected to the culture medium to undergo further chlorination, eventually arriving at danicalipin A (1.1). Since the chlorine atoms are introduced one by one, it is presumed that chlorination proceeds through free-radical processes, rather than electrophilic chlorination of an olefin.

45
1.4 Previous Synthetic Efforts

The limited availability of natural samples and difficulty associated with isolation was a significant barrier for in-depth evaluation of the chlorosulfolipids’ biological role. Their unique structure, along with their associated toxicity, prompted our group and others to engage in synthetic studies towards the chlorosulfolipids. The Vanderwal group was the first to report a methodology for diastereoselective dichlorination of linear allylic alcohols in a fashion that could provide a key motif present in mytilipin A.\textsuperscript{25} Shortly thereafter, the Yoshimitsu/Tanaka group described a strategy for preparing enantioenriched acyclic polychlorides via stereospecific deoxydichlorination of enantionenriched epoxides (Scheme 1.2).\textsuperscript{22}
Scheme 1.2 a. Vanderwal’s diastereoselective dichlorination of Z-allylic trichloroacetates to provide key motifs present in the chlorosulfolipids (highlighted) b. Tanaka and Yoshimitsu’s deoxydichlorination of epoxides

The first in class synthesis was disclosed in 2009 by Carreira’s group for the preparation of mytilipin A. Like many of the syntheses that came after, Carreira took advantage of alkene oxidation reactions to diastereoselectively incorporate the stereogenic chlorines.\(^{17}\) Chemoselective dichlorination of ethyl sorbate 1.17 was followed by reduction and protection of the resultant alcohol (Scheme 1.3). Diastereoselective dihydroxylation (5.6 : 1 \(dr\)) of the olefin provided 1.18. A clever manipulation of the diol 1.18 to the epoxide, followed by deprotection afforded 1.19. As their convergent step, a Wittig olefination with ylide 1.20 was employed to provide the desired Z olefin 1.21. It was envisioned that treatment of 1.21 with excess chloride in the presence of a Lewis acid would cause chloride displacement at the C11 allylic position to give the desired inversion of stereochemistry. Unfortunately, treatment of this epoxide with TMSCl gave the chlorohydrin 1.24 with net retention of stereochemistry at the C11 position, as determined by \(J\)-based configurational analysis. What is postulated to occur is anchimerically-assisted epoxide opening at the C11 position by one of the adjacent chlorides to give either of the chloronium intermediates 1.22 or 1.23. Exogenous chloride opens the high energy chloronium intermediate at the allylic C11 position to form chlorohydrin 1.24 as the result of double inversion of stereochemistry at the C11 position—or net retention overall. In a subsequent study, Carreira was able to show that both 1.22 and 1.23 can form, the four-membered chloronium 1.23 likely contributing the most.\(^{46}\) Halogen assisted epoxide openings have been known since 1971.\(^{47}\)
To circumvent this undesired reactivity, the Carreira group cleverly took advantage of this double inversion pathway by accessing the trans-epoxide isomer 1.25. Subjection to TMSCl now provided 1.27 the desired stereochemistry at C11 via the presumed intermediacy of chloronium 1.26. Dichlorination with Mioskowski’s reagent affords 1.29 with high diastereoselectivity, presumably...
under control of the C11 stereogenic center with minimization $A_{1,3}$-strain. Three steps were necessary to install the $E$-vinyl chloride and a subsequent sulfation provided $(\pm)$-mytilipin A in 1.3% overall yield in 10 steps.

The Carreira group later developed an asymmetric variant of their synthesis of mytilipin A (1.3) via (parallel) resolution of racemic dichloride 1.30 (Scheme 1.4).20 Sharpless asymmetric epoxidation of the allylic alcohol functional group afforded epoxide 1.19 in 1.3:1 $dr$; the enantiopurity of the desired diastereomer was moderate at 89:11 $er$.

**Scheme 1.4** Carreira’s use of the sharpless epoxidation for the asymmetric synthesis of mytilipin A

Almost concurrently, the Vanderwal lab disclosed the first synthesis of danicalipin A, confirming the relative stereochemistry, which at the time was unknown.26 Again taking advantage of alkene oxidation reactions, the synthesis began with easily accessible diene 1.31. A chemoselective dichlorination of the less electron-deficient olefin on 1.31, followed by diastereocontrolled dihydroxylation provided intermediate 1.32 (Scheme 1.5). After selective epoxide formation and reduction to the aldehyde 1.33, they were able to perform the key convergent step, a poorly diastereoselective Wittig olefination with the elaborated phosphonium salt 1.34 to yield 1.35. Chlorinolysis of the epoxide at the more activated C13 allylic position proceeded with inversion of stereochemistry to provide the desired stereotriad 1.36. This outcome was fortunate considering the difficulties Carreira’s group encountered with double inversion on similar substrates; however, diastereoselectivity issues were the primary cause of only a 46% yield for 1.36. A diastereoselective
hydrochlorination was required to install the remote C11 chlorine. The alkene 1.36 was iodochlorinated to provide a precursor to danicalipin A 1.37 with the correct regiochemistry and in modest diastereoselectivity. Deiodination and sulfation provided racemic danicalipin A in 1.2% overall yield over 12 steps.

Scheme 1.5 Vanderwal’s first generation synthesis of (±)-danicalipin A

Shortly thereafter the Vanderwal group disclosed an enantioselective synthesis of malhamensilipin A. A collaboration between the Vanderwal and Gerwick group refined the structure of malhamensilipin A; up until that point the relative stereochemistry was not known. A Sharpless asymmetric dihydroxylation was employed to access diol 1.38 in enantioenriched form (Scheme 1.6). Dichlorination of the nosylated intermediate 1.39 provided the chlorohydrin 1.40 in high diastereoselectivity. Conversion of 1.40 to the Z-allylic chloride 1.41 utilized a sequence of four steps already worked out from the danicalipin A synthesis, with a Wittig olefination being the
convergent step. Alkene dichlorination and desilylation with concomitant sulfation provided the bis-sulfate 1.42. A selective elimination of HCl was performed using LDA to provide (+)-malhamensilipin A in 1.0% overall yield in 12 steps.

**Scheme 1.6** Vanderwal’s enantioselective synthesis of (+)-malhamensilipin A

Other chlorosulfolipid syntheses include Yoshimitsu/Tanaka’s synthesis of mytilipin A using a 1,3-dipolar cycloaddition as the convergent step, Matsuda’s synthesis of danicalipin A, and Carreira’s tour de force synthesis of the proposed structure of mytilipin B—thereby determining the incorrectness of that structure.

**1.5 Conclusion**

Although effective, Vanderwal’s first-generation syntheses of 1.1 and 1.2 were fraught with several problems: (1) the critical convergent Wittig reaction was poorly stereoselective and somewhat erratic in terms of reproducibility; (2) the enantioselective route to malhamensilipin A could not be applied to danicalipin A because of a stereochemical difference in the targets; and (3) the routes were lengthy. The focus of this dissertation is a second-generation strategy that is applicable to chlorosulfolipids 1.1–1.3 in enantioenriched forms by virtue of a kinetic resolution of
chlorinated cis-vinyl epoxides. This approach also obviates the troublesome Wittig reaction, by way of a convergent Z-selective alkene cross metathesis reaction. The results are (1) for danicalipin A, eight steps racemic, nine steps enantioselective (previous best 12 steps racemic or 13 steps enantioselective); (2) for mytilipin A, seven steps racemic, eight steps enantioselective (previous best 10 steps racemic or 19 steps enantioselective); and (3) for malhamensilipin A, 11 steps formal enantioselective (previous best was our previous 12-step route, which was the only prior synthesis).

1.6 References


Chapter 2: General Approach to the Synthesis of Several Chlorosulfolipids

2.1 Synthesis Plan

As alluded to in the previous chapter, we were aiming for a shorter synthesis that could be generalized to targets 1.1–1.3 by taking advantage of the common stereotriad highlighted in Figure 1.1. Karl Bedke (PhD) and Chris Vanderwal became keenly interested in an approach involving diastereoselective carbonyl additions to α,β-dichloroaldehydes such as 2.3. Conceptually, this approach was attractive because these starting materials are easy to access—at least in racemic form—and additions to the aldehyde should be highly stereocontrolled. However, the poor stability of these aldehydes, which eliminate HCl easily, prevented our laboratory’s early attempts to use this tactic. To our knowledge, only Yoshimitsu and co-workers had successfully added nucleophiles to α,β-dichloroaldehydes2,3 prior to the work that we describe here.

The synthesis plan that was most attractive is shown in Scheme 2.1. Stereospecific anti-dichlorination of either an (E)- or a (Z)-allylic alcohol will lead to anti- or syn-dichloroalcohol products, respectively. Assuming high levels of 1,2-stereoinduction,2-4 a haloallylation reaction would afford either syn-halohydrin 2.4 or cis-vinyl epoxide 2.5, depending upon workup conditions. Either of these intermediates could be productive substrates for Z-selective alkene cross metathesis as a replacement for the Wittig olefination; the products that result would intersect with the late stages of two previous Vanderwal lab syntheses. The major impediments to the implementation of this plan were: (1) it was not certain that an efficient and stereoselective carbonyl addition to dichloroaldehydes would be possible; (2) there was no obvious way to render the synthesis enantioselective; and (3) Z-selective alkene cross metathesis was, at the time we began this work,
very much in its infancy and was not certain to work on such functionalized and potentially reactive substrates.

**Scheme 2.1** General approach to danicalipin A, malhamensilipin A, and mytilipin A featuring carbonyl additions to α,β-dichloroaldehydes and convergent Z-selective alkene cross metathesis

2.2 Results and Discussion

Because our lab had experience with its late-stage chemistry, we aimed to first apply our new strategy to an enantioselective synthesis of danicalipin A. Discussed are the solutions to the three key unknowns described above in the context of this target. Then the generality of the approach will be demonstrated with the syntheses of all three targets in subsequent sections.5,6

2.2.1 Additions to α,β-Dichloroaldehydes

For the new synthetic route, it was necessary to develop conditions for mild and highly diastereoselective haloallylation of α,β-dichloroaldehydes to establish an efficient route toward the requisite *cis*-vinyl epoxide of type 2.5. These studies were done by Karl Bedke (PhD). Initial attempts by Dr. Bedke at Grignard, organolithium, or alkali metal enolate additions to these aldehydes were met with failure, as were Lewis acid-catalyzed addition of π-nucleophiles. While the Yoshimitsu group had some success in this area,2,3 Carreira alludes to similar problems in their
disclosure of the mytilipin A synthesis. On the other hand, additions to α-chloroaldehydes were generally quite efficient and often stereoselective; these outcomes were not surprising given the lack of elimination pathways and the rather well-known stereocontrol imparted by α-acceptor groups on carbonyl additions. For example Dr. Bedke showed that the chloroallylation of α-chloroisovaleraldehyde 2.8 with (Z)-γ-chloroallylstannane 2.9 in the presence of BF₃·OEt₂ provided undesired syn,syn-2.10 with high diastereoselectivity (Scheme 2.2).

**Scheme 2.2 Chloroallylation of α-chloroaldehyde**

Not surprisingly, Bedke was not successful in extending this reaction type to electrophiles with β-chlorides. In contrast, 2.8 could be converted to desired anti,syn-2.10 by chloroallylation with (Z)-γ-chloroallylborane 2.11. However, the base-promoted epoxide formation surprisingly proceeded with poor site selectivity to give a mixture of constitutional isomers 2.12 and 2.13. Nonetheless, this haloallylborane reactivity could be extended to α,β-dichloroaldehydes (see below), and this outcome was the first hint that this type of electrophile tends to survive the milder conditions associated with closed transition structure allylations and related reactions. These observations were important in the eventual discovery by Bedke that the bromoallylaluminum reagent 2.17 was able to react with 2.16.
and produce the desired anti,syn product 2.18. It was found that basic workup of the reaction mixture delivered vinyl epoxide 2.19 in high yield as a single regioisomer. This initial result from Bedke was the starting point from which an attractive sequence was developed. Careful optimization of the reaction conditions was required, especially the Dess–Martin periodinane oxidation to limit the amount of β-chloride elimination. The sequence that resulted was able to deliver (±)-2.19 as a single regioisomer in 70% yield from the commercially available allylic precursor 2.14 in multigram scale with essentially perfect diastereoselectivity consistent with both the Felkin–Anh and Cornforth models (Scheme 2.3).

**Scheme 2.3 Synthesis of racemic cis-vinyl epoxide (±)-2.19**

2.2.2 Preparation of Enantioenriched Intermediates via Kinetic Resolution

Because we were clearly beholden to starting our synthesis from α,β-dichloroaldehydes, we required either enantioselective access to these key intermediates, or a means to resolve them if we were to render our synthesis enantioselective. Olefin dichlorination is a challenging reaction to render enantioselective owing to certain aspects of the mechanism. The first step of olefin dichlorination generates a chloronium intermediate 2.21 as a result of the olefin 2.20 reacting with an electrophilic source of chlorine. Even if there was a method for obtaining high facial selectivity to favor one
chloronium over the other, there remains a challenge of regioselective attack of the chloride to generate either enantiomer of the dichloride 2.22. Additionally, Denmark has shown there is the possibility for enantiodepletion of chloronium 2.21 via reversibility back to starting olefin, or by direct chlorenium transfer to another molecule of the olefin 2.20 (Scheme 2.4).\textsuperscript{13}

**Scheme 2.4** Mechanism of olefin dichlorination

Recently the groups of Nicolaou\textsuperscript{14} and Burns\textsuperscript{15,16} have made impressive steps forward in this area. Both groups discovered a combination of a chiral catalyst and chlorine equivalent that allows for enantioselective dichlorination on an array of allylic alcohols. The use of a chiral catalyst appears to allow for facially selective chloronium formation; regioselectivity is controlled by the bias of the substrates (Scheme 2.5). While Nicolaou’s methodology was amenable to a range of substrates, it worked best for cinnamyl alcohols and required a relatively high catalyst loading. On the other hand, Burns’s methodology had only one example of enantioselective olefin dichlorination, with the main body of the work focusing on dibrominations and bromochlorinations.
Scheme 2.5 Examples of enantioselective dichlorination by \( a. \) the Nicolaou group \( b. \) the Burns group

Although technology for asymmetric alkene chlorination is improving, there was not at the time a method that would prove economical enough for the preparation of highly enantioenriched dichloroalcohols to service a natural product synthesis endeavor of this type.

Scott Halpern (MSc 2008) spent some time trying to develop just such a reaction, but with no success.\(^{17}\) His attempt to obtain enantioenriched material via enantioselective dichlorination with Cinchona alkaloid-derived chiral variants of Mioskowski’s reagent (Et\(_4\)NCl\(_3\))\(^{18}\) or resolution of dichlorinated primary alcohols by peptide-catalyzed\(^{19}\) or enzymatic means were unsuccessful. Of course, highly effective examples of enzymatic resolution of chiral primary alcohols are few.\(^{20}\)

Clearly, either resolution methods of later stage intermediates or Yoshimitsu’s elegant stereospecific dichlorodeoxygenation reactions of epoxides\(^4\) were the most promising ways to access enantioenriched intermediates. Owing to the single additional step involved in resolutions compared with the multiple steps involved in the epoxide-based strategy, we took the former approach to solve our problem.

Performing a kinetic resolution to isolate enriched starting material is a very attractive process given that the \( ee \) of the starting material increases with conversion. Even with modest selectivity factors (\( S = k_{rel} = k_{\text{fast}}/k_{\text{slow}} \)), highly enantioenriched starting materials can be achieved by increasing conversion beyond 50\%.

For example, with a modest selectivity factor of 10, recovered substrate can be isolated
in 95% ee and 34% yield. Kinetic resolutions that intend to isolate enantioenriched products are inherently more challenging. To achieve the same result of 95% ee and 34% yield for isolated product a selectivity factor of 63 is required (Figure 2.1).

**Figure 2.1 a.** Plot of enantiomeric excess of recovered substrate as a function of conversion for representative $k_{rel}$ values as calculated using the equation $k_{rel} = \ln[(1 - c)(1 - ee_{SM})]/\ln[(1 - c)(1 + ee_{SM})]$

**Figure 2.1 b.** Plot of enantiomeric excess of product as a function of conversion for representative $k_{rel}$ values as calculated using the equation $k_{rel} = \ln[1 - c(1 + ee_P)]/\ln[1 - c(1 - ee_P)]$ Reprinted with permission. Copyright 2002 American Chemical Society.

We considered resolving racemic vinyl epoxide 2.19 derived from diastereoselective haloallylation/epoxide formation of the α,β-dichloroaldehyde (Scheme 2.3). Vinyl epoxide 2.19 has a strong bias for regiocontrol of ring opening; clearly the allylic terminus is activated while the other epoxide carbon is deactivated by the proximal chlorides. Therefore, we postulated that some of the many available enantioselective meso-epoxide desymmetrization protocols should be plausibly extended to kinetic resolution of substrates of type 2.19.

We began with Jacobsen’s epoxide opening chemistry, using highly reactive $(R,R)$-(oligosalen)Co catalysts. To the best of our knowledge, resolutions of internal epoxides with the Jacobsen system have not been reported; however, we felt that the cis-vinyl epoxide might be a close structural mimic of competent cyclic meso-epoxides that are frequently desymmetrized using Jacobsen chemistry. Surprisingly, substrate 2.19 proved unreactive toward nucleophiles such as
water, phenol, or benzyl alcohol under published conditions for desymmetrization of *meso*-epoxides. For reasons that we do not understand, Denmark’s catalytic system for desymmetrization of *meso*-epoxides via ring-opening chlorinolysis,\(^{26,27}\) using the “Lewis base activation of Lewis acids” concept,\(^{28}\) proved much more successful. In the original Denmark group study, *meso*-stilbene oxide \(^{2.27}\) was effectively desymmetrized in the presence of a chiral phosphoramidate Lewis base catalyst \((R)-2.28\) and SiCl\(_4\), a weak Lewis acid, to afford the syn-1,2-chlorohydrin \((1S,2S)-2.30\) in high enantiopurity (Scheme 2.6a).\(^{26}\) Later, it was found that the dimeric phosphoramidate Lewis base \((R,R)-2.29\), which is typically more selective for other SiCl\(_4\)-mediated enantioselective transformations, provided \((1S,2S)-2.30\) with notably diminished enantiopurity.\(^{27}\) The stereochemical outcome of desymmetrization of *meso*-epoxide suggested that the \((R)\)-BINAM-derived phosphoramidate Lewis base catalysts would enrich our cis-vinyl epoxide reactants in the desired enantiomer by selectively catalyzing ring-opening chlorinolysis of the undesired enantiomer.
Scheme 2.6 a. Denmark’s desymmetrization of meso-epoxides b. Preliminary study of chiral lewis base-catalyzed kinetic resolution of cis-vinyl epoxide (±)-2.19. Selectivity factor, \( S = \frac{k_{\text{fast}}}{k_{\text{slow}}} = \ln[(1 - \text{conversion})(1 - ee)]/\ln[(1 - \text{conversion})(1 + ee)] \)

c. Chiral lewis bases studied for kinetic resolution

Studies performed by Dr. Won-jin Chung discovered the cis-vinyl epoxide (±)-2.19 to be less reactive than meso-epoxides, probably because of the more sterically congested environment presented by the proximal chlorine bearing carbons. Consequently, the kinetic resolution with (R)-2.28 was carried out at slightly elevated temperature (−50 °C) with higher catalyst loading (20 mol%) (Scheme 2.6b). Unfortunately, the resolution with (R)-2.28 proceeded with poor selectivity (selectivity factor, \( S = 4 \)). Surprisingly, in contrast to Denmark’s result, the dimeric chiral Lewis base (R,R)-2.29 was more selective (\( S = 14 \)) for our kinetic resolution than the monomeric chiral Lewis base (R)-2.28. Interestingly and unexpectedly, the resolved vinyl epoxide from the kinetic resolutions with (R)-2.28 and (R,R)-2.29 were enriched in the opposite enantiomers. Other chiral Lewis bases such as trans-cyclohexanediamine-derived phosphoramide (R,R)-2.31 and (R)-BINAPO


((R)-2.32) were also tested by Dr. Chung. These Lewis bases were more reactive than (R)-2.28 or (R,R)-2.29 but virtually unselective (S < 3). Clearly, we had a good lead with catalyst (R,R)-2.29 at this point.

Dr. Won-jin Chung performed an extensive optimization study on the kinetic resolution of (±)-2.19. He found that the selectivity is highly dependent on reaction temperature (Table 2.1, entry 1), catalyst loading, reaction time (entry 2), the presence of Et₄NCl as an additive (entry 3), and reaction concentration (entry 4-7). The amounts of SiCl₄ and i-Pr₂NEt seem to have little effect on the conversion and selectivity. Eventually, an ideal 53% conversion was achieved with 20 mol% of (S,S)-2.29 after 24 h at 0.2 M, and the desired enantiomer of unreacted vinyl epoxide (−)-2.19 was isolated in 43% yield with 97.3:2.7 er on a preparative scale (entry 8 and Scheme 2.7). The catalyst could be fully recovered after reaction.

Table 2.1 Optimization of kinetic resolution of (±)-2.19 a

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<th>entry</th>
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<th>time</th>
<th>conversion</th>
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<th>e.r. (product)</th>
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<td>3.9:96.1</td>
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<td>48 h</td>
<td>61%</td>
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<td>22.2:77.8</td>
<td>9</td>
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<td>48 h</td>
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<td>33</td>
</tr>
<tr>
<td>5</td>
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<td>24 h</td>
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<td>83.7:16.3</td>
<td>10.0:90.0</td>
<td>18</td>
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<td>27.9:72.1</td>
<td>88.1:11.9</td>
<td>27</td>
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a All reactions employed 1.0 equiv of SiCl₄ and 0.1 equiv of i-Pr₂NEt on 0.1–2.0 mmol scale.
b Determined by 1H NMR analysis. c Determined by CSP-GC. d Determined by CSP-SFC after 2,4-dinitrobenzoylation. e 20 mol% of cat. f 1.0 equiv. Et₄NCl. g Preparative scale, using (S,S)-2.29, to preferentially recover (−)-2.19.
The optimized kinetic resolution conditions were next applied to a substrate that was destined for the enantioselective synthesis of mytilipin A. In collaboration with Dr. Won-jin Chung the cis-vinyl epoxide (±)-2.38 was prepared in a similar manner to that used to make (±)-2.19 (Scheme 2.8). (E)-Crotyl alcohol (2.34) was treated with molecular chlorine in the presence of Et₄NCl to give the anti-1,2-dichloride (±)-2.35. Oxidation with the Dess–Martin periodinane followed by a careful workup afforded the sensitive and volatile α,β-dichloroaldehyde (±)-2.36 in crude form, which was immediately converted to volatile cis-vinyl epoxide (±)-2.38 via bromoallylalumination and epoxide formation, again with near perfect diastereocontrol. The moderate yield in this case can be attributed to volatility of the intermediate aldehyde and the vinyl epoxide product.

Surprisingly, the kinetic resolution of (±)-2.38, which differs only by alkyl chain length compared to (±)-2.19, was only moderately selective with catalyst (R,R)-2.29. Under the optimized conditions
developed for (±)-2.19, a selectivity factor of only 6 was obtained (Table 2.2, entry 1). Although it was possible to recover (+)-2.38 with an improved enantiopurity at higher conversion (entry 2), a more practical level of selectivity was desired. Similar to the case of (±)-2.19, Dr. Chung was again able to improve the selectivity factor by lowering the concentration. As a result of his efforts a selectivity factor of 13 at 57% conversion was realized at 0.1 M concentration, and enantioenriched (+)-2.38 was isolated in 93.4:6.6 er and 43% yield (entry 4 and Scheme 2.9a). Curiously, Dr. Chung found that it was difficult to reliably analyze the enantiopurity of the chlorohydrin product (+)-2.39 because of apparently facile selective sublimation of the major enantiomer under vacuum, which resulted in enantiodepletion of the sample (Scheme 2.9b).29

<table>
<thead>
<tr>
<th>entry</th>
<th>concentration</th>
<th>time</th>
<th>conversion</th>
<th>e.r. (reactant)</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2 M</td>
<td>24 h</td>
<td>56%</td>
<td>84:6:16:4</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>0.2 M</td>
<td>36 h</td>
<td>65%</td>
<td>92:4:7:6*</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>0.15 M</td>
<td>72 h</td>
<td>65%</td>
<td>94:8:5:2</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>0.1 M</td>
<td>72 h</td>
<td>57%</td>
<td>93:4:6:6</td>
<td>13</td>
</tr>
</tbody>
</table>

* All reactions employed 1.0 equiv of SiCl₄ and 0.1 equiv of i-Pr₂NEt and were conducted on 0.25–0.54 mmol scale. * Determined by 'H NMR analysis. *

Table 2.2 Optimization of kinetic resolution of (±)-2.38*
Scheme 2.9 *a*. Optimized kinetic resolution conditions for (±)-2.38 *b*. Enantiodepletion of (+)-2.38 under high vacuum

The same kinetic resolution strategy was also examined for the enantioselective synthesis of (+)-malhamensilipin A. The corresponding cis-vinyl epoxide (±)-2.44, which differs from substrates 2.19 and 2.38 by virtue of its syn-1,2-dichloride moiety, was prepared from (Z)-2-undecen-1-ol 2.40 via the same sequence used for previous substrates (Scheme 2.10a). Unfortunately, (±)-2.44 was considerably less reactive toward chlorinolysis than the other vinyl epoxide substrates, and the enantioselectivity was very poor (Scheme 2.10b). Under the general conditions with 20 mol% of (R,R)-2.29, the resolution proceeded to only 15% conversion even after 72 h and afforded a selectivity factor of only 4. Modified reaction conditions with higher concentrations, higher temperatures, or addition of exogenous chloride, while likely to accelerate the reaction, would equally likely attenuate the already very low enantioselectivity, as we had previously observed in the study of (±)-2.19. When (±)-2.44 was resolved with the typically more reactive (S)-BINAP ((S)-2.32), a much higher reaction rate was indeed observed. Contrary to previous cases, the selectivity factor was also improved, although it was still moderate (S = 8–9). From a preparative scale reaction, the resolved vinyl epoxide (−)-2.44 was obtained in 3.4:96.6 e.r and 34% yield.
Several related chiral bis(phosphine oxide)s such as (S)-Tol-BINAPO, (S)-H₈-BINAPO, and (R)-SEGPHOS dioxide were also tested, but the selectivity was not improved.

**Scheme 2.10 a.** Synthesis of racemic cis-vinyl epoxide (±)-2.44

**Scheme 2.10 b.** Kinetic resolution of (±)-2.44

2.2.3 Convergent Z-Selective Alkene Cross Metathesis

Concurrent with the development of an effective kinetic resolution method, the key convergent metathesis step was investigated with (±)-2.19, a potential precursor to danicalipin A. At the time of conception of our metathesis-based second-generation approach, only the first hint that Z-selective alkene cross metathesis was a viable reaction had appeared in the literature.³⁰ Moreover, whereas a Z-configured alkene is required en route to malhamensilipin A and mytilipin A so that stereospecific anti-dichlorination would afford the correct relative syn-configuration (at C11/C12 and C9/C10, respectively), it was not obviously a necessity for danicalipin A because of the
unchlorinated carbon at C12. Therefore, the feasibility of the alkene cross metathesis approach was initially evaluated with normal alkene metathesis catalysts.

Two different orders of operations were considered for alkene cross metathesis and ring-opening chlorinolysis (Scheme 2.11). The left-hand sequence involves the alkene cross metathesis of a vinyl epoxide 2.5 followed by chlorinolysis of the resulting internal alkenyl epoxide, which might be plagued by double inversion at the allylic center and $S_N2'$ side reactions, as seen in previous studies. On the other hand, the right-hand sequence is initiated with chlorinolysis of the terminal vinyl epoxide, which might proceed as a clean $S_N2$ reaction under certain conditions, for example, the “racemic version” of the vinyl epoxide chlorinolysis resolution using SiCl$_4$ and an achiral Lewis base catalyst such as HMPA. The resulting allylic chlorohydrin 2.47 would then be a potential substrate for subsequent alkene cross metathesis to deliver 2.48. With the latter sequence, the enantioenriched 1,2-chlorohydrin product from the kinetic resolution could also be conveniently utilized for the synthesis of enantiomeric chlorosulfolipids.

**Scheme 2.11** Possible orders of operations for alkene cross metathesis and ring-opening chlorinolysis

Electron-poor allylic chloride (±)-2.33 underwent alkene cross metathesis with 1-decene in the presence of 10 mol% of the Grubbs second-generation catalyst (G II) at room temperature to afford
the \((E)\)-alkene product \(2.49\) in 43\% yield along with dimeric side products (Scheme 2.12); because of the relatively complex crude reaction mixture, it was difficult to determine the inherent \(E/Z\) selectivity of this reaction. The Hoveyda–Grubbs second-generation catalyst (\(\text{HG II}\)) promoted slower but cleaner alkene cross metathesis to give an 84:16 \(E:Z\) mixture of alkene isomers in 85\% conversion and 60\% yield of isomerically pure \(2.49\). Unfortunately, iodochlorination of \(2.49\) with ICl provided a complex crude mixture (not shown), in contrast to the case of the corresponding \(Z\)-isomer that had been iodochlorinated with high efficiency in our first-generation approach, although with low diastereoselectivity.

Scheme 2.12 Alkene cross metathesis of \((\pm)\)-2.33

\[ \begin{align*}
&\text{C}_8\text{H}_{17} \ (10 \text{ equiv}) \\
&\text{HG II} \ (10 \text{ mol\%}), \\
&\text{PhMe, rt, 40 h} \\
\text{complete conversion} \\
\text{43\% yield of E isomer} \\
\end{align*} \]

To generate the more desirable \((Z)\)-alkene isomer, \(Z\)-selective alkene cross metathesis of allylic chloride \(2.33\) with various terminal alkene partners in the presence of recently developed Grubbs cycloadamantyl catalyst \(2.50,^{31-45}\) which was generously provided first by the Grubbs group and
later by Materia, was investigated. However, not only 2.33 but also hydroxy-protected substrates and the less chlorinated substrate 2.52 exhibited no reactivity (Scheme 2.13). An interesting mode of reactivity was uncovered when the same coupling was attempted on allylic bromide 2.54. Instead of producing the cross-coupled product, the aryl alkylidene ligand on 2.50 was incorporated into the starting material exclusively as the E olefin. Given that ruthenium(II) compounds are known to form allylic ruthenium(IV) complexes, presumably the mechanism for the formation of 2.56 proceeds through the intermediacy of 2.55, followed by reductive elimination. Clearly the adamantyl catalyst is highly effective for the Z selective cross-metathesis for some substrates, but also prone to undesired decomposition.

**Scheme 2.13** Alkene cross metathesis of allylic chloride and bromide substrates using Z-selective catalyst 2.50
In an attempt to take advantage of the increased effective concentration of the intramolecular reaction, compound 2.57 was prepared and subjected to metathesis conditions. Under conventional ring closing metathesis conditions using (GII) followed by silyl cleavage to diol 2.58 a 4:1 diastereomeric mixture favoring the E alkene was observed. However under Z-selective conditions using 2.50 (C633) no desired product 2.59 was observed after siloxy cleavage (Scheme 2.14).

Scheme 2.14 Tethered olefin metathesis strategy towards danicalipin A

Ruthenium metathesis catalysts are clearly able to execute cross metatheses of allylic chlorides; at this stage, we have no reasonable understanding of the apparent limitation of the Z-selective catalysts toward allylic chlorides and bromides, nor do we know if it is a truly general limitation.

Alternatively, the corresponding cis-vinyl epoxide was examined as a substrate for alkene cross metathesis. Similarly to the corresponding allylic chloride, cis-vinyl epoxide (±)-2.19 underwent alkene cross metathesis with 1-decene in the presence of 10 mol% of G II to afford 2.60 with moderate 82:18 E:Z-selectivity (Scheme 2.15). Unlike the case of chlorohydrin substrates, it was difficult to separate the internal alkenyl epoxide product from the unreacted terminal vinyl epoxide reactant. These compounds were isolated as a mixture (estimated yields of the product and the recovered reactant: ~57% and 10%, respectively based on NMR integration). In contrast, a complex
mixture was obtained from the similar reaction with HG II. While the desired product was not detected, one of the major components in the crude mixture was identified as the unsaturated chloroaldehyde 2.61, which implies the formation of α,β-dichloroaldehyde 2.16 (Scheme 2.3) under the reaction conditions. Additionally, the presence of chlorohydrin 2.62 as a minor component in the crude mixture further suggests the formation of 2.16 followed by elimination of HCl, which is presumably responsible for epoxide chlorinolysis of a small amount of desired alkene cross metathesis product. The formation of 2.61 was confirmed from the reactions between 2.19 and HG II (10 and 100 mol%) in the absence of other metathesis partners. At this stage, we cannot put forth a reasonable mechanism for this interesting three-carbon degradation of vinyl epoxides. We have not investigated the generality of this reaction type.

**Scheme 2.15 Alkene cross metathesis between 2.19 and simple terminal alkenes**

Gratifyingly, cis-vinyl epoxide 2.19 turned out to be a competent substrate for Z-selective alkene cross metathesis. In the presence of 1 mol% of catalyst 2.50, 2.19 underwent alkene cross metathesis with an excess of 1-hexene to 12% conversion at 35 °C in 1 h (Scheme 2.16). The Z-isomer of vinyl epoxide 2.63 was produced with exquisite selectivity. Such exceptionally high Z-selectivity had only
been rarely observed with this catalyst.\textsuperscript{31–45} Other solvents such as toluene or dichloromethane had no significant impact on the conversion and selectivity. The catalytic activity was typically lost within a few hours, and the reactions would proceed no further. The conversion could be improved to about 50–60\% (NMR estimate) with higher loading of catalyst (10 mol\%), and the use of chlorinated solvents such as dichloromethane or 1,2-dichloroethane proved beneficial because of the poor solubility of 2.50 in other solvents. However, the decomposition of the starting vinyl epoxide was a serious side reaction, and significant amounts of an as yet unidentified decomposition product were formed.

Scheme 2.16 Z-Selective alkene cross metathesis of 2.19 with 1-hexene

With this preliminary success in hand, we turned to the use of the relevant alkene 2.67 as the metathesis partner, which was made from known aldehyde 2.64\textsuperscript{47} via a slight modification of Yoshimitsu’s procedure\textsuperscript{3} as shown in Scheme 2.17a. This high molecular weight compound could not be used in as large excess as the model alkenes owing to effects on reaction concentration; initial reactions suffered from very low efficiencies, and the decomposition of the starting vinyl epoxide remained problematic. The related alkene 2.66, with a free hydroxyl group and attendant lower molecular weight that could potentially be used in greater excess, was unreactive (Scheme 2.17b).
Scheme 2.17 a. Preparation of potential alkene cross metathesis partners 2.66 and 2.67 for the synthesis of danicalipin A and malhamensilipin A. b. Z-selective alkene cross metathesis of 2.19 for the synthesis of danicalipin A (all compounds shown are racemic).

To achieve higher conversion and suppress the decomposition, an extensive optimization of the reaction conditions was conducted, with helpful assistance and suggestions from Professor Bob Grubbs and his graduate students at Caltech. A variety of reaction solvents including tetrahydrofuran, diethyl ether, tert-butyl methyl ether, toluene, chlorobenzene, hexafluorobenzene, α,α,α-trifluorotoluene, and octafluorotoluene, as well as neat conditions were employed, but the reaction efficiency was not improved. The reaction was even slower at room
temperature, and performing the reaction at higher temperature (60 °C) only resulted in greater decomposition.

A wide range of additives were also evaluated by Dr. Chung. Amine bases such as \(i\text{-Pr}_2\text{NEt}\) and di-\textit{tert}-butylpyridine promoted decomposition. 1,4-Benzoinone, known to scavenge ruthenium hydride species\textsuperscript{49} that might be formed during reaction and cause decomposition, only attenuated the catalytic reactivity of 2.50. The reaction became slightly cleaner in the presence of 3 or 4 Å molecular sieves, but substrate decomposition could not be completely avoided. Ti(O\textit{i}-\textit{Pr})\textsubscript{4}\textsuperscript{50} and hexachloroethane,\textsuperscript{51} which have been used to improve the reactivity of other alkene cross metathesis reactions, had no influence on the reaction.

Portionwise addition of catalyst and 1-hexene also provided no advantage. We hoped that removal of ethylene from the reaction mixture would shift the cross metathesis equilibrium and drive these reactions to higher conversion. Therefore, the reaction was carried out under static vacuum, continuous vacuum, and in an open vessel inside a glovebox, but to no avail. More rigorous removal of ethylene was attempted by vigorously bubbling argon through the reaction mixture, and gratifyingly, the formation of the unknown was finally prevented. Under optimized conditions, with 10 mol\% of 2.50, (\(\pm\))-2.69 was obtained in 19\% yield along with 74\% recovered starting material (Scheme 2.17b). It was more challenging to suppress the decomposition with higher catalyst loadings, and the mass balance was poorer. The decomposition could be minimized by slowing down the reaction rate via a portionwise addition of catalyst, giving the product 2.69 in 29\% yield with 40\% recovered starting material using 30 mol\% of 2.50. Although we were unable to achieve more than the equivalent of a single turnover, this sequence still stands as a marked improvement over the previous Wittig-based route. Access to enantioenriched 2.69 now requires only five steps,
compared with our previous eight-step approach that afforded racemic material. As a result, this moderate success completed a much shorter, enantioselective formal synthesis of danicalipin A because of the interception of intermediate **2.69** from our first-generation synthesis. However, more improvements in the end-game were still possible (see below).

Convergent Z-selective alkene cross metathesis for mytilipin A with the corresponding *cis*-vinyl epoxide **2.38** proceeded similarly to the corresponding reaction for danicalipin A. Alkene metathesis partner **2.72** was obtained in two steps from 8-bromo-1-octene (**2.70**) via formylation of Grignard reagent followed by Takai-Utimoto chloroolefination (Scheme 2.18). The convergent metathesis reactions were carried out with vigorous bubbling of argon to prevent the decomposition of starting vinyl epoxide, and the desired alkene (±)-(Z)-**2.73** was produced as a single geometrical isomer. Again, we were unable to achieve more than a single turnover with 10–30 mol% of catalyst **2.50** (Table 2.3, entries 1 and 2). Dr Chung found the use of fluorinated solvents such as α,α,α-trifluorotoluene**48** did not result in any improvement (entry 3). Unfortunately, higher loading of catalyst only resulted in significant loss of mass balance and the yield of product was only marginally improved (entries 4 and 5). Despite the low efficiency of the Z-selective alkene cross metathesis, the direct incorporation of the vinyl chloride is a marked improvement over previous syntheses because it eliminates at least three postconvergence steps. Cross metathesis partner **2.72** might appear upon cursory analysis to be poised for side reactivity because as a 1,9-diene cyclooctene formation could occur via ring-closing metathesis. However, vinyl chlorides are relatively slow to react in metathesis processes, and cyclo-octene formation can also be a sluggish reaction. Almost certainly, however, the high kinetic selectivity of catalyst **2.50** for (Z)-alkenes is presumably the most important factor that prevents reaction with the (E)-vinyl chloride in either RCM or cross metathesis events.
Unfortunately, the convergent Z-selective alkene cross metathesis was even less efficient for malhamensilipin A. The metathesis product (+)-2.74 was isolated only in 19% yield from the reaction of (−)-2.44 with 2.67 under the analogous conditions to those used for danicalipin A (Scheme 2.19). Cursory attempts to improve the efficiency of this reaction were unsuccessful. For reasons explained below, the improvement of this convergent step was not a priority.

Scheme 2.19 Z-selective alkene cross metathesis for the synthesis of malhamensilipin A
While admittedly not as efficient as desired, the convergent Z-selective alkene cross metathesis is noteworthy for its complete diastereoselectivity in all cases examined. To see if the extremely high selectivity we observed was general for cis-vinyl epoxides, as well as to investigate the low catalytic activity of 2.50 with respect to the specific chlorinated cases relevant to the chlorosulfolipids, Dr. Chung tested the reactivity of unchlorinated cis-vinyl epoxide 2.77 with 1-decene (Scheme 2.20b). In the presence of 10 mol% of 2.50, complete conversion to (Z)-vinyl epoxide 2.78 was observed (83% isolated yield, >20:1 Z:E). Even with only 1 mol% of catalyst, the reaction proceeded to 46% conversion and the product was isolated in 43% yield with equal selectivity. Therefore, it appears that cis-vinyl epoxides are subject to highly Z-selective alkene cross metathesis with 2.50, and that the poor efficiency observed in the convergent steps for chlorosulfolipids is likely specific to chlorinated substrates. Recently, the Grubbs group also demonstrated that vinyl epoxides are excellent substrates for Z-selective metathesis using these catalysts.\textsuperscript{35}

**Scheme 2.20 a.** Synthesis of simple vinyl epoxide 2.77. **b.** Z-selective alkene cross metathesis of (±)-2.77
2.2.4 Postconvergent Manipulations and Completion of the Syntheses

Completion of the synthesis of (+)-danicalipin A took advantage of a similar reaction sequence to that previously developed in the context of the Vanderwal lab’s first-generation approach (Scheme 1.5). Lewis acid-mediated chlorinolysis of the internal alkenyl epoxide 2.69 typically afforded a diastereomeric mixture of the desired $S_N2$ product 2.79 and the double inversion $^7\text{,}^52$ product 2.80 as well as the constitutional isomer 2.81 formed via $S_N2'$ substitution (Scheme 2.21a). The extent of side product formation was highly dependent on the choice of Lewis acid and the concentration of chloride anion. Because exclusive $S_N2$ reactivity was observed from the reaction of terminal cis-vinyl epoxide with SiCl$_4$ in the presence of HMPA, a combination of SiCl$_4$ and a number of Lewis base activators including pyridine, DMAP, pyridine $N$-oxide, HMPA, DMPU, DMI, and TMU was evaluated with or without Et$_4$NCl. In all cases, a variable amount of side products were produced and a useful level of selectivity was not accomplished (90:10–31:69 dr, 2–50% $S_N2'$). Both undesired pathways were reasonably attenuated when the epoxide was opened using dry HCl; however, high selectivity was desired specifically for the exclusion of double inversion product 2.80, which is more difficult to separate from the desired product. Double inversion could be completely overcome by employing BF$_3$·OEt$_2$ at $−78$ °C with a high concentration of Et$_4$NCl. Despite the presence of a rather large amount of $S_N2'$ product 2.81, the desired isomer 2.79 could be isolated in 73% yield as a single diastereomer. A major problem of our first-generation synthesis was the poorly diastereoselective iodochlorination reaction of 2.79 ($类似1.8:1$ dr), which was compounded further by the very painstaking separation of diastereomers at that stage or after deiodination. Attempts to directly hydrochlorinate the unactivated alkene under iron-mediated radical hydrofunctionalization conditions recently reported by Boger$^53$ was unsuccessful, probably because of the low reactivity of the electron-deficient alkene. We found that transient
introduction of a trimethylsilyl group on the C14 hydroxyl permitted high diastereoselectivity (95:5 dr) in the iodochlorination, and because the silyl group could be introduced and removed in the same pot, this result had a significantly positive impact on the synthesis. Overall, the new approach facilitated a nine-step synthesis of enantioenriched (+)-danicalipin A (4.6% overall yield), which is a significant improvement over our 12-step racemic first-generation synthesis.

Scheme 2.21 a. Completion of the synthesis of (+)-danicalipin A. b. Completion of the synthesis of (−)-mytilipin A

Completion of the synthesis of mytilipin A required only three postconvergence steps (Scheme 2.21b). BF$_3$·OEt$_2$-mediated vinyl epoxide chlorinolysis with inversion of configuration proceeded with exclusive diastereoselectivity and delivered diene 2.82. Dichlorination of the electron-deficient
allylic chloride afforded hexachloride 2.83 in 86% yield with high diastereoselectivity (93:7 dr of crude product, purified to 97:3) and complete chemoselectivity with respect to the isolated vinyl chloride. Sulfation of the secondary alcohol according to Carreira’s conditions completed the synthesis of mytilipin A. In this way, racemic chlorosulfolipid could be accessed in 8.6% yield over the seven linear steps sequence, and enantioenriched mytilipin A is available via a longest linear sequence of eight steps (3.7% overall yield). These results compare favorably to the previously reported syntheses.

It is indeed fortuitous that we chose to first pursue danicalipin A with this new approach. The choice of malhamensilipin A as a first target could easily have discouraged us from pursuing this strategy. Although, as described above, this strategy led to much improved syntheses of mytilipin A and danicalipin A, there was ultimately little improvement in the synthesis of malhamensilipin A, for which we had already established an enantioselective synthesis, via the same number of steps, and for which the Wittig reaction was not improved upon with the metathesis option. Therefore, while we are pleased to claim a formal enantioselective synthesis of malhamensilipin A as part of this second-generation, general strategy for chlorosulfolipid synthesis, we would suggest that our first enantioselective synthesis of this single target would likely be the preferred method to access samples of this natural product. However, if new catalysts become available that can better effect these challenging Z-selective cross metatheses, and if a truly effective method for asymmetric dichlorination of allylic alcohols is discovered, the strategy described here would be hard to beat for any of these three chlorosulfolipid targets. Indeed, this approach has the distinct advantage that it can be rendered enantioselective without recourse to resolution once asymmetric catalysis technology is developed for allylic alcohol dichlorination.
2.3 Facets of diastereoselectivity in halogenation of chlorinated lipids bearing an internal olefin

In the course of attempting to improve diastereoselectivity for the iodochlorination of alkene 2.79a, we began to notice some interesting trends. Our early experiments sought to make use of E-homoallylic alcohol 2.84, since it could be accessed by a high yielding conventional cross metathesis. The predominant product of iodochlorination was the undesired 1,3-syn product 2.85a, presumably formed by chloride attack on the anti-iodonium intermediate (Scheme 2.22). The diastereoselectivity could be reinforced to favor the undesired 1,3-syn product in near perfect diastereoselectivity by subjecting the corresponding E-homoallylic silyl ether 2.84b to the same reaction conditions. In no instances could we get a preponderance of the desired 1,3-anti product from the E olefin. It was these results that confirmed to us the necessity of accessing the Z-olefin.

As mentioned above it was found that the diastereoselectivity of iodochlorination of Z-homoallylic alcohol 2.79a en route to danicalipin A could be improved considerably simply by using the silylated variant 2.79b. A remarkable reversal in diastereoselectivity was observed when homoallylic alcohol 2.79a was subjected to dichlorination conditions to produce the 1,3-syn product 2.87a, presumably through the intermediacy of the syn chloronium. However, in a reversal of diastereoselectivity, the silylated variant 2.79b produced the 1,3-anti product (not shown) under the dichlorination reaction conditions. For reasons we do not understand, silylation of the homoallylic alcohol tends to favor the anti halonium intermediate; although a Curtin–Hammett scenario could also be in effect.
The chlorosulfolipids possess preferred solution state conformations that avoid syn-pentane interactions. It is possible that the changes of diastereoselectivity observed in this chemical series by silyl protection at the homoallylic alcohol position are due to changes in the preferred solution state conformation.

### 2.4 Conclusions

Presented is a concise and general approach for the enantioselective synthesis of three chlorosulfolipid targets that takes strategic advantage of a common stereotriad. Diastereoselective carbonyl addition to sensitive α,β-dichloroaldehydes, Z-selective alkene cross metatheses, and kinetic resolution of chlorinated vinyl epoxides were key advances that permitted success in this second-generation approach. Enantioenriched danicalipin A, mytilipin A, and malhamensilipin A were accessed in nine, eight, and 11 steps, respectively.5,6
After an extensive effort on the part of the Vanderwal lab and others to study the chlorosulfolipids, enough was known to allow for Dr. Won-jin Chung and myself to bring to a fruition the most practical strategy to date for enantioselective synthesis of several chlorosulfolipids. This strategy featured a diastereoselective bromoallylation, an idea conceived by Karl Bedke (PhD), and a kinetic resolution that was only practical after extensive optimization by Dr. Won-jin Chung. This strategy also showcased the current state of the art of Z-selective olefin metathesis and its first use in the context of complex synthesis.

2.5 Experimental Procedures

General Experimental Protocols

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Reaction solvents including dichloromethane, toluene, N,N-dimethylformamide, and tetrahydrofuran were dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon. Dichloroethane (DCE) was heated to reflux over CaH2 for 3 h, distilled under argon, and stored over 3 Å molecular sieves prior to use. Column chromatography was performed using 60 Å (0.040–0.063 mm) mesh silica gel (SiO2). The following reagents were distilled from the indicated drying agents under argon prior to use: 2,2,6,6-tetramethylpiperidine (Na), allyl bromide (CaH2), triethylamine (CaH2), N,N-diisopropylethylamine (CaH2), trimethylsilyl chloride (TMSCl, CaH2), and ethylene diamine (CaH2). Silicon tetrachloride was heated at reflux for 2 h under a flow of argon and then distilled prior to use. Z-Selective Grubbs cycloadamantyl catalyst (2.50, Materia) was stored in the glovebox and used as received. Dimeric Denmark catalysts ((R,R)-2.29 and (S,S)-2.29, Obiter) were used as received and recovered by
recrystallization from boiling benzene. \((E)-2-\text{Nonen-1-ol (2.14), boron trifluoride diethyl etherate, and tri-}n\-butyltin hydride were distilled prior to use. Tetraethylammonium chloride was heated to reflux in benzene with a Dean–Stark trap for 3 h and dried at 0.25 mmHg before use. Chlorine gas, Dess–Martin periodinane, diethylaluminum chloride, \(n\)-butyllithium, imidazole, iodine monochloride (1.0 M in CH\(_2\)Cl\(_2\)), camphorsulfonic acid (CSA), triethylborane (1.0 M in THF), chlorosulfonic acid, nickel(II) acetate tetrahydrate, sodium borohydride, magnesium (20–100 mesh), 1,2-dibromoethane, 1-bromo-10-undecene, \(N\)-chlorosuccinimide, \(t\)-butyldimethylsilyl chloride, and paraformaldehyde were used without further purification. Tetraethylammonium trichloride\(^{18}\) and \((S\)-BINAPO\(^{54}\) were prepared according to literature procedures.

\(^1\)H and \(^{13}\)C spectra were referenced to residual solvent (CDCl\(_3\): 7.26 ppm, \(^1\)H, 77.16 ppm, \(^{13}\)C; CD\(_3\)OD: 3.31 ppm, \(^1\)H, 49.00 ppm, \(^{13}\)C; (CD\(_3\))\(_2\)CO: 2.05 ppm, \(^1\)H, 29.84 ppm, \(^{13}\)C). Chemical shifts are reported in parts per million, and multiplicities are indicated by \(s\) (singlet), \(d\) (doublet), \(t\) (triplet), \(q\) (quartet), \(m\) (multiplet), br \(s\) (broad singlet), and app (apparent). Coupling constants, \(J\), are reported in Hertz. Infrared (IR) spectra were recorded on an FT-IR instrument on NaCl plates, and peaks are reported in cm\(^{-1}\). High-resolution mass spectra (HRMS) data are reported in the form of \((m/z)\). Kugelrohr distillation temperatures reported are air bath temperatures (ABT). Visualization of analytical thin-layer chromatography was accomplished with UV(254) and potassium permanganate (KMnO\(_4\)) or \(p\)-anisaldehyde staining solutions. Optical rotation data were obtained on a digital polarimeter and are reported as follows: concentration \((c = g/100 \text{ mL})\) and solvent. Analytical gas chromatography (CSP-GC) was performed on a gas chromatograph equipped with a flame ionization detector and a dimethylated \(\beta\)-cyclodextrin (B-DM, 30 m) capillary column. The injector temperature and the detector temperature were 200 °C with a split ratio of approximately 100:1.
Synthesis of Danicalipin A

(±)-(2S,3R)-2,3-Dichloro-1-nonanol (2.15): To a stirred solution of Et$_4$NCl (6.63 g, 40.0 mmol) and (E)-2-nonen-1-ol (2.84 g, 20.0 mmol) in CH$_2$Cl$_2$ (60 mL) was bubbled Cl$_2$ at 0 °C until the reaction mixture turned yellow (~2 min). Ethylene was bubbled until the yellow color disappeared (~2 min). The resulting colorless solution was diluted with CH$_2$Cl$_2$ (50 mL) and shaken with a mixture of saturated aqueous NaHCO$_3$ solution (50 mL) and saturated aqueous Na$_2$S$_2$O$_3$ solution (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (50 mL). The combined organic extracts were shaken with saturated aqueous NaCl solution (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (50 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo (25 mmHg). The residue was purified by bulb-to-bulb distillation under reduced pressure (0.25 mmHg, ABT 123–126 °C) to afford (±)-2.15 (4.04 g, 95%, contained ~1.5% of 1,3-dichloro-2-nonanol) as a colorless oil. Data for (±)-2.15: $^1$H NMR (600 MHz, CDCl$_3$) δ 4.12 (app td, $J$ = 8.7, 8.7, 2.7 Hz, 1H), 4.09–4.06 (m, 1H), 4.024 (d, $J$ = 6.6 Hz, 1H), 4.017 (d, $J$ = 6.6 Hz, 1H), 2.11–2.02 (m, 1H), 1.97 (app t, $J$ = 6.9, 6.9 Hz, 1H), 1.82–1.75 (m, 1H), 1.64–1.54 (m, 1H), 1.48–1.39 (m, 1H), 1.39–1.23 (m, 6H), 0.89 (dd, $J$ = 6.8, 6.8 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 66.4, 64.5, 61.8, 34.9, 31.6, 28.6, 25.5, 22.5, 14.0; IR (thin film) 3390, 2924, 2858, 1463, 1455, 1434, 1379, 1066, 725, 655 cm$^{-1}$; HRMS (Cl-TOF) $m/z$ calcd for C$_9$H$_{18}$Cl$_2$ONH$_4$ [M + NH$_4$]$^+$ 230.1078, found 230.1071.
(±)-(2S,3R)-2,3-Dichlorononanal (2.16): To a stirred suspension of (±)-2.15 (2.13 g, 10.0 mmol) and NaHCO$_3$ (2.52 g, 30.0 mmol) in CH$_2$Cl$_2$(10 mL, saturated with H$_2$O) was added Dess–Martin periodinane (6.36 g, 15.0 mmol) slowly over 1 min at 0 °C under air. After stirring for 10 min, the ice bath was removed and the reaction mixture was stirred at rt for 30 min prior to the addition of n-pentane (100 mL). The resulting mixture was filtered, washed with saturated aqueous NaHCO$_3$ (50 mL), dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo (25 mmHg) to give 2.16 (1.99 g) as a pale yellow oil. The crude material was used directly for the next reaction without further purification (~3% 2-chloro-2-nonenal).$^{56}$ Data for (±)-2.16: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 9.43 (d, $J$ = 3.1 Hz, 1H), 4.25 (dd, $J$ = 7.4, 3.1 Hz, 1H), 4.24–4.21 (m, 1H), 2.02–1.97 (m, 1H), 1.84–1.77 (m, 1H), 1.63–1.54 (m, 1H), 1.48–1.39 (m, 1H), 1.39–1.27 (m, 6H), 0.90 (dd, $J$ = 6.9, 6.9 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 191.4, 64.9, 59.8, 34.0, 31.5, 28.5, 25.5, 22.5, 14.0; IR (thin film) 2926, 2858, 1734, 1458 cm$^{-1}$; HRMS (CI-TOF) $m/z$ calcd for C$_9$H$_{15}$ClONH$_4$ [M – HCl + NH$_4$]$^+$ 192.1155, found 192.1158.

(±)-(3S,4S,5S,6R)-5,6-Dichloro-3,4-epoxy-1-dodecene (2.19): To a stirred solution of TMP (3.71 mL, 22.0 mmol) in THF (50 mL) was added n-BuLi (2.50 M in hexanes, 8.40 mL, 21.0 mmol) at −78 °C. After being stirred for 30 min, the LiTMP solution was cannulated into a solution of allyl bromide (1.82 mL, 21.0 mmol) and Et$_2$AlCl (1.0 M in hexanes, 40.0 mL, 40.0 mmol) in THF (100 mL) at −78 °C over 5 min. The resulting solution was stored at −78 °C, while (±)-2.16 was prepared
(see above). A solution of (±)-2.16 in THF (10 mL + rinsed with 5 mL × 2) was added dropwise over 15 min. After being stirred at −78 °C for 4 h, the reaction mixture was poured into an ice-cold 5 M aq NaOH solution (200 mL). Et₄NCl (17 mg, 0.10 mmol) was added. The biphasic mixture was vigorously stirred at rt for 1 h prior to the dilution with n-pentane (100 mL) and filtration. The organic layer was separated, and the aqueous layer was extracted with n-pentane (100 mL × 2). The combined organic extracts were washed with saturated aqueous NH₄Cl solution (200 mL × 2), dried over Na₂SO₄, filtered, and concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO₂, φ = 5.0 cm, l = 13.5 cm, n-pentane/CH₂Cl₂, 9/1, Rf = 0.29, p-anisaldehyde) and bulb-to-bulb distillation under reduced pressure (0.25 mmHg, ABT 123–127 °C) to give (±)-2.19 (1.89 g, 75% from (±)-2.15, 98:2 dr) as a colorless oil. Data for (±)-2.19: ¹H NMR (600 MHz, CDCl₃) δ 5.82 (ddd, J = 17.1, 10.6, 5.6 Hz, 1H), 5.52 (d, J = 17.1 Hz, 1H), 5.45 (d, J = 10.7 Hz, 1H), 4.21 (ddd, J = 9.4, 4.6, 4.1 Hz, 1H), 3.76 (dd, J = 9.0, 4.2 Hz, 1H), 3.57 (app t, J = 4.9, 4.9 Hz, 1H), 3.46 (dd, J = 9.0, 4.3 Hz, 1H), 1.98–1.87 (m, 2H), 1.65–1.59 (m, 1H), 1.47–1.39 (m, 1H), 1.36–1.26 (m, 6H), 0.89 (dd, J = 6.9, 6.9 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 130.4, 121.2, 65.2, 60.6, 57.7, 56.0, 34.5, 31.6, 28.6, 26.5, 22.5, 14.0; IR (thin film) 2956, 2928, 2858, 1463, 1455, 1250, 981, 934, 783, 668, 597 cm⁻¹; HRMS (CI-TOF) m/z calcd for C₁₂H₂₀₃Cl₂ONH₄ [M + NH₄]⁺ 268.1235, found 268.1236.

(−)-(3S,4S,5S,6R)-5,6-Dichloro-3,4-epoxy-1-dodecene (2.19), (−)-(3S,4R,5R,6S)-3,5,6-trichloro-1-dodecen-4-ol (2.33): To a stirred solution of (±)-2.19 (126 mg, 0.502 mmol) and (S,S)-2.29 (84 mg, 0.10 mmol) in CH₂Cl₂(2.5 mL) were added i-Pr₂NEt (9 μL, 0.05 mmol) and SiCl₄ (57 μL, 0.50
mmol) at −78 °C. After 24 h, a solution of CH₃OH/Et₃N/CH₂Cl₂ (1/1/5, 4 mL) was added quickly at −78 °C. The resulting solution was vigorously stirred with a saturated aqueous NaHCO₃ solution (20 mL) at rt for 2 h prior to filtration. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (10 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo (25 mmHg). (S,S)-2.29 was recovered from the residue by column chromatography (SiO₂, φ = 2.2 cm, l = 7 cm, CH₂Cl₂/i-PrOH, 10/1, Rf = 0.37, UV). The fractions that contained 2.19 and 2.33 were combined and purified by column chromatography (SiO₂, φ = 2.2 cm, l = 11 cm, n-pentane/CH₂Cl₂, 8/1 to 4/1, p-anisaldehyde) to give (−)-2.33 (70 mg, 49%, Rf = 0.12 in 8/1, 88.1:11.9 er) as a colorless oil and (−)-2.19 as a colorless oil, which was purified again by column chromatography (54 mg, 43%, Rf = 0.30 in 8/1, 2.7:97.3 er). Data for (−)-2.19: [α]D²⁶ = −29.9 (c 1.00, CHCl₃); GC (B-DM, 30 psi, 145 °C) tR 15.5 min (2.7%), 16.5 min (97.3%). Data for (−)-2.33: [α]D²⁵ = −60.6 (c 1.00, CHCl₃); GC (B-DM, 30 psi, 165 °C) tR 18.5 min (88.1%), 19.1 min (11.9%); ¹H NMR (500 MHz, CDCl₃) δ 6.03 (ddd, J = 16.9, 10.2, 7.7 Hz, 1H), 5.49 (d, J = 16.9 Hz, 1H), 5.35 (d, J = 10.2 Hz, 1H), 5.07 (d, J = 7.6 Hz, 1H), 4.51 (app dt, J = 10.5, 2.7, 2.7 Hz, 1H), 4.31 (dd, J = 9.4, 2.7 Hz, 1H), 3.89 (app td, J = 9.8, 9.8, 1.3 Hz, 1H), 2.23 (d, J = 9.9 Hz, 1H), 1.92–1.83 (m, 1H), 1.83–1.74 (m, 1H), 1.68–1.58 (m, 1H), 1.46–1.23 (m, 7H), 0.89 (app t, J= 6.6, 6.6 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 134.4, 119.6, 74.5, 66.5, 65.0, 62.5, 32.4, 31.6, 28.6, 26.5, 22.6, 14.0; IR (thin film) 3540, 2956, 2927, 2857, 1465, 1379, 1265, 1096, 1069, 987, 935 cm⁻¹; HRMS (CI-TOF) m/z calcd for C₁₂H₂₁³⁵Cl₃ONH₄ [M + NH₄]⁺ 304.1002, found 304.1000.
The solvents were bubbled with argon for 15 min before use. To a stirred solution of (−)-2.19 (52 mg, 0.21 mmol) and 2.67 (152 mg, 0.414 mmol) in DCE (210 μL) in a test tube (12 mm × 75 mm) was added a solution of 2.50 (39 mg, 0.062 mmol) in CH₂Cl₂ (210 μL) in three portions (0, 0.5, 1.0 h) at 35 °C while the reaction mixture was vigorously bubbled with argon (saturated with DCE). After being stirred at 35 °C with argon bubbling for an additional 2 h, the reaction mixture was cooled to rt, filtered through silica gel (ϕ = 2.2 cm, l = 9 cm, CH₂Cl₂, 40 mL), and concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO₂, ϕ = 3.8 cm, l = 15 cm, n-pentane/CH₂Cl₂, 8/1, Rf = 0.24, p-anisaldehyde) to give (+)-2.69 (35 mg, 29%, >20:1 = Z:E) as a colorless oil. Data for (+)-2.69: [α]D²⁶ = +14.2 (c 1.00, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 5.86 (app dt, J = 10.9, 7.6 Hz, 7.6, 1H), 5.26–5.20 (m, 1H), 4.21 (ddd, J = 9.6, 4.4, 4.0 Hz, 1H), 3.76 (dd, J = 9.1, 4.0 Hz, 1H), 3.74 (dd, J = 7.9, 4.3 Hz, 1H), 3.44 (dd, J = 9.1, 4.2 Hz, 1H), 2.27–2.19 (m, 2H), 2.19–2.14 (m, 2H), 1.99–1.86 (m, 2H), 1.66–1.55 (m, 3H), 1.46–1.39 (m, 3H), 1.39–1.26 (m, 14H), 0.91 (s, 9H), 0.89 (app t, J = 6.9, 6.9 Hz, 3H), 0.11 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 139.6, 121.5, 93.5, 72.1, 65.2, 61.5, 57.4, 52.5, 43.5, 34.3, 31.6, 29.29, 29.27, 29.26, 29.1, 29.0, 28.6, 28.1, 26.5, 25.7, 24.7, 22.5, 18.3, 14.0, −5.4.
(+)-\((7R,8S,9S,10R,11Z)-22\text{-}\text{tert-Butyldimethylsiloxy}-7,8,10,21,21\text{-}\text{pentachloro}-11\text{-}\text{docosen}-9\text{-}\text{ol} \) (2.79): To a stirred solution of (+)-2.69 (35 mg, 0.059 mmol) and Et₄NCl (30 mg, 0.18 mmol) in CH₂Cl₂ (240 µL) was added BF₃·OEt₂ (15 µL, 0.12 mmol) at −78 °C. After being stirred for 1 h, the reaction mixture was poured into an ice-cold saturated aqueous NaHCO₃ solution (10 mL). To the biphasic mixture were added CH₂Cl₂ (10 mL) and H₂O (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (10 mL × 2). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo (25 mmHg). The residue was purified by column chromatography \((\text{SiO}_2, \phi = 1.5 \text{ cm}, \ l = 9 \text{ cm}, \ n\text{-}\text{pentane}/\text{CH}_2\text{Cl}_2, \ 5/1 \text{ to } 3/1 \text{ to } 1/1, \ p\text{-}\text{anisaldehyde})\) to give (+)-2.79 (27 mg, 73%, \(R_f = 0.25 \text{ in } 3/1, >20:1 \text{ dr})\) as a colorless oil and \(S\text{N}_2\text{ product} \) 2.81 (9.6 mg, 26%, \(R_f = 0.33 \text{ and } 0.24 \text{ in } 1/1, 6:4 \text{ dr})\) as a colorless oil. Data for (+)-2.79: 

\[ [\alpha]_D^{25} = +62.5 \ (c \ 1.00, \ \text{CHCl}_3); \ \text{\text{H NMR}} \ (600 \text{ MHz, CDCl}_3) \ \delta \ 5.73 \text{ (app t, } J = 10.3, \ 10.3 \text{ Hz, 1H),}\]
\[ 5.66 \text{ (app dt, } J = 10.7, \ 7.4, \ 7.4 \text{ Hz, 1H),}\]
\[ 5.38 \text{ (dd, } J = 9.9, \ 1.7 \text{ Hz, 1H),}\]
\[ 4.49 \text{ (app dt, } J = 10.3, \ 2.9, \ 2.9 \text{ Hz, 1H),}\]
\[ 4.29 \text{ (dd, } J = 9.0, \ 3.1 \text{ Hz, 1H),}\]
\[ 3.92 \text{ (s, 2H),}\]
\[ 3.83–3.78 \text{ (m, 1H),}\]
\[ 2.34 \text{ (d, } J = 10.5 \text{ Hz, 1H),}\]
\[ 2.21–2.09 \text{ (m, 4H),}\]
\[ 1.91–1.83 \text{ (m, 1H),}\]
\[ 1.83–1.76 \text{ (m, 1H),}\]
\[ 1.67–1.62 \text{ (m, 1H),}\]
\[ 1.61–1.56 \text{ (m, 2H),}\]
\[ 1.46–1.36 \text{ (m, 3H),}\]
\[ 1.36–1.25 \text{ (m, 14H),}\]
\[ 0.91 \text{ (s, 9H),}\]
\[ 0.89 \text{ (app t, } J = 6.8, \ 6.8 \text{ Hz, 3H),}\]
\[ 0.11 \text{ (s, 6H);}\]
\[ \text{\text{C NMR}} \ (126 \text{ MHz, CDCl}_3) \ \delta \ 135.7, \ 125.8, \ 93.5, \ 75.1, \ 66.8, \ 62.4, \ 60.1, \ 43.5, \ 32.5, \ 31.6, \ 29.3, \ 29.2, \ 29.1, \ 29.0 \text{ (2C),}\]
\[ 28.6, \ 27.6, \ 26.5, \ 25.7, \ 24.7, \ 22.6, \ 18.3, \ 14.0, –5.4. \]

Data for 2.81 (a 6:4 mixture of diastereomers): 

\[ \text{\text{H NMR}} \ (600 \text{ MHz, CDCl}_3) \ \delta \ 5.97–5.90 \text{ (m, 1H),}\]
\[ 5.79 \text{ (ddd, } J = 15.2, \ 13.9, \ 6.8, \ 1\text{H),}\]
\[ 4.77 \text{ (app td, } J = 7.3, \ 7.3, \ 3.9 \text{ Hz, 0.4H),}\]
\[ 4.72 \text{ (app td, } J = 7.2, \ 7.2, \ 4.3 \text{ Hz, 0.6H),}\]
\[ 4.39 \text{ (app quintet, } J = 7.4, \ 7.4, \ 7.4, \ 7.4 \text{ Hz, 1H),}\]
\[ 4.18 \text{ (ddd, } J = 8.8, \ 6.7, \ 4.1 \text{ Hz, 1H),}\]
\[ 3.92 \text{ (s, 2H),}\]
\[ 3.91–3.88\]
(m, 1H), 2.20–2.14 (m, 2H), 2.13–2.04 (m, 2H), 1.89–1.73 (m, 3H), 1.65–1.51 (m, 3H), 1.50–1.37 (m, 3H), 1.37–1.23 (m, 14H), 0.91 (s, 9H), 0.89 (app t, $J = 6.8, 6.8$ Hz, 3H), 0.11 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 136.0, 135.7, 128.22, 128.17, 93.5, 72.1, 72.0, 71.7, 69.4, 69.1, 61.9, 61.7, 61.6, 43.5, 38.4, 38.3, 34.7, 34.5, 31.6, 29.30, 29.26, 29.0, 28.9, 28.61, 28.60, 26.43, 26.35, 25.7, 25.3, 25.2, 24.7, 22.5, 18.3, 14.1, −5.4; IR (thin film) 3403, 2929, 2857, 1463, 1256, 1153, 1120, 970, 840, 780 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for C$_{28}$H$_{53}$$^{35}$Cl$_3$O$_2$SiNa [M + Na]$^+$ 647.2155, found 647.2143.

$^{(-)}$-(11S,12R,13S,14R,15S,16R)-1-tert-Butyldimethylsiloxy-2,2,11,13,15,16-hexachloro-14-hydroxy-12-iododocosane (2.80):$^{52}$ To a stirred solution of (+)-2.79 (27 mg, 0.043 mmol) and imidazole (8.8 mg, 0.13 mmol) in CH$_2$Cl$_2$(430 μL) was added TMSCl (11 μL, 0.086 mmol) at rt. After being stirred for 10 min, the reaction mixture was cooled to −78 °C and ICl (1.0 M in CH$_2$Cl$_2$, 215 μL, 0.215 mmol) was added. After being stirred for 20 min at −78 °C, a solution of CSA (100 mg, 0.43 mmol) in CH$_3$OH (645 μL) was added and the cold bath was removed. After being stirred for 30 min, the brown solution was poured into a stirred mixture of saturated aqueous NaHCO$_3$ solution (5 mL) and saturated aqueous Na$_2$S$_2$O$_3$ solution (5 mL). The resulting colorless biphasic mixture was diluted with CH$_2$Cl$_2$ (10 mL) and H$_2$O (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (10 mL × 2). The combined organic extracts were washed with saturated aqueous NH$_4$Cl solution (20 mL), and the aqueous layer was extracted with CH$_2$Cl$_2$ (10 mL × 2). The combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO$_2$, n-C$_6$H$_{13}$
ϕ = 1.1 cm, l = 5.5 cm, n-pentane/\text{CH}_2\text{Cl}_2, 5/1 to 3/1, R_f = 0.29 in 3/1, p-anisaldehyde) to give (−)-2.80 (28 mg, 82%, 95:5 dr) as a colorless oil. Data for (−)-2.80: [α]_D^{26} = −7.6 (c 1.00, CHCl₃); \textsuperscript{1}H NMR (600 MHz, CDCl₃) δ 4.98 (d, J = 10.9 Hz, 1H), 4.72 (app t, J = 10.6, 10.6 Hz, 1H), 4.56 (dd, J = 10.9, 1.8 Hz, 1H), 4.48 (app dt, J = 10.5, 2.6, 2.6 Hz, 1H), 4.38 (dd, J = 9.8, 2.4 Hz, 1H), 3.92 (s, 2H), 3.75–3.71 (m, 1H), 2.19–2.16 (m, 2H), 2.14 (d, J = 11.3 Hz, 1H), 2.04–1.97 (m, 1H), 1.97–1.88 (m, 1H), 1.83–1.78 (m, 1H), 1.77–1.71 (m, 1H), 1.69–1.62 (m, 1H), 1.62–1.56 (m, 2H), 1.53–1.46 (m, 1H), 1.46–1.38 (m, 3H), 1.38–1.27 (m, 13H), 0.92 (s, 9H), 0.90 (app t, J = 6.8, 6.8 Hz, 3H), 0.11 (s, 6H); \textsuperscript{13}C NMR (126 MHz, CDCl₃) δ 93.5, 74.6, 72.1, 66.3, 66.0, 62.9, 62.8, 43.5, 42.6, 40.6, 32.8, 31.6, 29.2 (2C), 29.0, 28.9, 28.6, 26.6, 26.2, 25.7, 24.7, 22.6, 18.3, 14.1, −5.3.

(+)-(11S,13S,14R,15S,16R)-1-\textit{tert}-Butyldimethylsiloxy-2,2,11,13,15,16-hexachloro-14-hydroxydocosane (2.81):

Toluene was bubbled with argon for 20 min before use. To a stirred solution of (−)-2.80 (28 mg, 0.035 mmol) in toluene (355 μL) were added n-Bu₃SnH (11 μL, 0.041 mmol, 99% pure by \textsuperscript{1}H NMR in C₆D₆)\textsuperscript{59} and Et₃B (1.0 M in THF, 7 μL, 0.007 mmol) at −78 °C. After being stirred for 2 h at −78 °C, n-pentane (3.55 mL) was added and the resulting solution was concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO₂, ϕ = 1.1 cm, l = 5.5 cm, n-pentane/\text{CH}_2\text{Cl}_2, 1/0 to 4/1, R_f = 0.25 in 4/1, p-anisaldehyde) to give (+)-2.81 (21.5 mg, 91%) as a colorless oil. Data for (+)-2.81: [α]_D^{25} = +34.3 (c 1.00, CHCl₃); \textsuperscript{1}H NMR (600 MHz, CDCl₃) δ 4.96 (d, J = 10.3 Hz, 1H), 4.51 (app dt, J = 10.6, 2.4, 2.4 Hz, 1H), 4.30 (dd, J = 9.7, 2.4 Hz, 1H), 4.17–4.13 (m, 1H), 3.92 (s, 2H), 3.77 (app t, J = 10.7, 10.7 Hz, 1H), 2.35–2.28 (m, 1H), 2.20–2.16 (m, 2H), 2.16 (d, J = 11.6 Hz, 1H), 2.02–1.95 (m, 1H), 1.94–1.85 (m, 1H), 1.83–1.73
(+)-Danicalipin A Disodium Salt (1.1): To a stirred solution of (+)-2.81 (21.5 mg, 0.0324 mmol) in CH₂Cl₂ (650 μL) was added ClSO₃H (5 drops) via a Pasteur pipet at rt under air. After being stirred for 10 min, the reaction mixture was slowly poured into a vigorously stirred mixture of a saturated aqueous NaHCO₃ solution (6.5 mL) and solid NaHCO₃ (650 mg). The resulting heterogeneous mixture was diluted with EtOH (26 mL), filtered, and concentrated in vacuo (30 mmHg). The residue was suspended in THF (20 mL), filtered, and concentrated in vacuo (25 mmHg). The residue purified by column chromatography (SiO₂, φ = 2.2 cm, l = 14.5 cm, CH₂Cl₂/CH₃OH, 3/1, Rf = 0.38, p-anisaldehyde) to give (+)-1.1 (23.4 mg, 96%) as a colorless amorphous solid. Data for (+)-1.1: [α]D₂⁵ = +34.2 (c 2.34, CH₃OH) (lit. [α]D²⁶ +33.0 (c 0.40, CH₃OH),³ [α]D²⁸ +31.5 (c 0.25, CH₃OH),⁶ [α]D²⁵ +12.8 (c 0.2, CH₃OH)⁶¹; ¹H NMR (600 MHz, CD₃OD) δ 4.89 (d, J = 11.2 Hz, 1H), 4.75 (d, J = 10.7 Hz, 1H), 4.55 (d, J = 10.2 Hz, 1H), 4.45 (dd, J = 10.2, 1.5 Hz, 1H), 4.31 (s, 2H), 4.23–4.19 (m, 1H), 2.56–2.49 (m, 1H), 2.27–2.24 (m, 2H), 2.15–2.06 (m, 1H), 1.99–1.92 (m, 1H), 1.85–1.76 (m, 2H), 1.76–1.69 (m, 1H), 1.69–1.62 (m, 2H), 1.61–1.52 (m, 2H), 1.51–1.42 (m, 2H), 1.42–1.27 (m, 14H), 0.90 (app t, J = 6.9, 6.9 Hz, 3H); ¹³C NMR (126 MHz, CD₃OD, 313 K) δ 91.3, 80.9, 75.6, 68.4, 63.3, 62.4, 62.2, 45.5, 45.1, 39.9, 33.5, 32.9, 30.4, 30.3, 30.07, 30.05, 30.0,
The analytical data for (+)-1.1 were in agreement with literature precedent.\textsuperscript{3,52,60,61}

**Synthesis of Malhamensilipin A**

(Z)-2-Undec-1-ol (2.40): To a stirred solution of Ni(OAc)$_2$·4H$_2$O (9.12 g, 36.7 mmol) in CH$_3$OH (500 mL) was added NaBH$_4$ (1.38 g, 36.7 mmol) portionwise over 5 min at 0 °C. The blue solution immediately turned black upon addition of NaBH$_4$. After being stirred for an additional 5 min, the ice bath was removed and ethylene diamine (4.90 mL, 36.7 mmol) was added. After being stirred for 5 min, a solution of undec-2-yn-1-ol\textsuperscript{62} (24.7 g, 147 mmol) in CH$_3$OH (230 mL) was added. The reaction mixture was quickly purged with H$_2$ three times and stirred overnight under a balloon of H$_2$ prior to the dilution with H$_2$O (100 mL) and n-pentane (100 mL). After filtration through Celite, the organic layer was separated and the aqueous layer was extracted with n-pentane (100 mL × 3). The combined organic extracts were washed with H$_2$O (50 mL) and saturated aqueous NaCl solution (50 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo (5 mmHg) to afford 2.40 (25.0 g, 98%) as a colorless oil. The crude material was used for the next reaction without any further purification. Data for 2.40: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 5.62–5.52 (m, 2H), 4.19 (d, $J = 6.4$ Hz, 2H), 2.07 (q, $J = 7.2$ Hz, 2H), 1.38–1.32 (m, 2H), 1.32–1.23 (m, 10H), 0.88 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 133.5, 128.4, 58.8, 32.0, 29.8, 29.6, 29.42, 29.38, 27.6, 22.8, 14.3; IR (thin film) 3347, 3938, 3857, 1015 cm$^{-1}$; HRMS (CI-TOF) m/z calcd for C$_{11}$H$_{22}$ONH$_4$ [M + NH$_4$]$^+$ 188.2014, found 188.2023.
(±)-(2S,3S)-2,3-Dichloro-1-undecanol (2.41): To a stirred solution of 2.40 (4.96 g, 29.1 mmol) in CH₂Cl₂ (70 mL) was added Et₄NCl₃ (13.8 g, 58.3 mmol) portionwise over 5 min at rt. After the yellow color disappeared over the course of 10 min, another portion of Et₄NCl₃ (6.89 g, 29.1 mmol) was added portionwise over 3 min. After being stirred for 30 min, the reaction mixture was poured into a mixture of saturated aqueous NaHCO₃ solution (15 mL) and saturated aqueous Na₂S₂O₃ solution (15 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes (30 mL × 3). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo (5 mmHg). The residue was purified by column chromatography (150 mL of SiO₂, 10% EtOAc/hexanes, R_f = 0.6 in 30% EtOAc/hexanes, KMnO₄) to give (±)-2.41 (5.79 g, 82%) as a colorless oil. Data for (±)-2.41: ¹H NMR (500 MHz, CDCl₃) δ 4.22 (ddd, J = 8.1, 5.4, 2.6 Hz, 1H), 4.18 (m, 1H), 3.95 (ddd, J = 11.9, 7.7, 6.0 Hz, 1H), 3.89 (ddd, J = 12.1, 7.5, 5.6 Hz, 1H), 3.94 (dd, J = 7.7, 5.4 Hz, 1H), 1.90–1.84 (m, 2H), 1.57–1.51 (m, 1H), 1.44–1.22 (m, 11H), 0.88 (app t, J = 6.6, 6.6 Hz, 3H); ¹³C (126 MHz, CDCl₃) δ 65.6, 64.7, 62.2, 35.3, 32.0, 29.5, 29.3, 29.1, 26.7, 22.8, 14.3; IR (thin film) 3363, 3923, 2855, 1455, 1041 cm⁻¹; HRMS (CI-TOF) m/z calcd for C₁₁H₂₂³⁵Cl₂ONH₄ [M + NH₄]⁺ 258.1392, found 258.1401.

(±)-(2S,3S)-2,3-Dichloroundecanal (2.42): To a stirred suspension of (±)-2.41 (2.20 g, 9.12 mmol) and NaHCO₃ (2.30 g, 27.4 mmol) in CH₂Cl₂ (46 mL, saturated with H₂O) was added Dess–Martin periodinane (5.80 g, 13.7 mmol) portionwise over 1 min at 0 °C under air. After being stirred for 5
min, the ice bath was removed and the reaction mixture was stirred at rt for 25 min prior to the addition of hexanes (20 mL) and saturated aqueous NaHCO₃ solution (100 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes (50 mL × 3). The combined organic extracts were filtered, dried over MgSO₄, filtered, and concentrated in vacuo (5 mmHg) to give (±)-2.42 as a pale yellow oil. The crude material was generally used directly for the next reaction within 30 min and without further purification (it was often contaminated with up to 5% 2-chloro-2-undecenal). Data for (±)-2.42: ¹H NMR (500 MHz, CDCl₃) δ 9.55 (s, 1H), 4.40 (app s, 2H), 1.92–1.86 (m, 2H), 1.55–1.48 (m, 1H), 1.40–1.22 (m, 11H), 0.88 (t, J = 7.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 194.8, 67.0, 60.1, 35.1, 31.8, 29.3, 29.1, 28.8, 26.1, 22.6, 14.1; IR (thin film) 2927, 2856, 1736, 1465 cm⁻¹; HRMS (ESI-TOF) m/z calcd for C₁₁H₁₉ClONa [M – HCl + Na]⁺ 225.1022, found 225.1013.

(±)-(3S,4S,5S,6S)-5,6-Dichloro-3,4-epoxy-1-tetradecene (2.44): To a stirred solution of TMP (3.39 mL, 20.1 mmol) in THF (46 mL) was added n-BuLi (2.47 M in hexanes, 7.75 mL, 19.2 mmol) at −78 °C. After being stirred for 15 min, the LiTMP solution was cannulated into a solution of allyl bromide (1.66 mL, 19.2 mmol) and Et₂AlCl (1.0 M in hexanes, 36.5 mL, 36.5 mmol) in THF (46 mL) at −78 °C over 15 min. The resulting solution was stored at −78 °C, while (±)-2.42 was prepared (see above). A solution of (±)-2.42 in THF (10 mL + rinsed with 8 mL × 2) was added dropwise down the side of the flask. After being stirred at −78 °C for 5 h, the cooling bath was removed and a 6 M aq NaOH solution (100 mL) was added. After stirring vigorously for 1 h, the biphasic mixture was diluted with hexanes (100 mL) and shaken in a separatory funnel. The organic
layer was separated, and the aqueous layer was extracted with hexanes (100 mL × 3). The combined organic extracts were washed with saturated aqueous NaCl solution (50 mL × 3), filtered through silica gel (CH$_2$Cl$_2$, 300 mL), and concentrated in vacuo (5 mmHg). The residue was purified by column chromatography (500 mL of SiO$_2$, 5% CH$_2$Cl$_2$/hexanes, $R_f$ = 0.2, KMnO$_4$) and bulb-to-bulb distillation under reduced pressure (0.1 mmHg, ABT 150 °C) to give (±)-2.44 as a colorless oil (1.83 g, 72% from (±)-2.41). Data for (±)-2.44: $^1$H NMR (500 MHz, CDCl$_3$) δ 5.82 (ddd, $J$ = 17.0, 10.6, 5.3 Hz, 1H), 5.49 (d, $J$ = 17.2 Hz, 1H), 5.45 (d, $J$ = 10.7 Hz, 1H), 4.26 (ddd, $J$ = 8.3, 4.9, 2.7 Hz, 1H), 3.67 (dd, $J$ = 8.9, 2.7 Hz, 1H), 3.64 (app t, $J$ = 4.7 Hz, 1H), 3.54 (dd, $J$ = 9.7, 4.7 Hz, 1H), 1.94 (app dtd, $J$ = 14.2, 9.5, 4.8 Hz, 1H), 1.83, (app ddt, $J$ = 14.0, 10.1, 5.4 Hz, 1H), 1.58–1.50, (m, 1H), 1.43–1.35 (m, 1H), 1.35–1.22 (m, 10H), 0.88 (app t, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 130.5, 121.3, 63.5, 60.4, 58.6, 57.4, 35.8, 32.0, 29.5, 29.3, 29.1, 26.5, 22.8, 14.3; IR (thin film) 2926, 2855, 932 cm$^{-1}$; HRMS (Cl-TOF) m/z calcd for C$_{14}$H$_{24}$Cl$_2$ONH$_4$ [M + NH$_4$]$^+$ 296.1548, found 296.1560.

\[ \text{(-)-(3S,4S,5S,6S)-5,6-Dichloro-3,4-epoxy-1-tetradecene (2.44), (+)-(3S,4R,5R,6R)-3,5,6-trichloro-1-tetradecen-4-ol (2.45)} \]

To a stirred solution of (±)-2.44 (500 mg, 1.79 mmol) and (S)-BINAP (234 mg, 0.358 mmol) in CH$_2$Cl$_2$ (36 mL) were added $i$-Pr$_2$NEt (31.0 μL, 0.179 mmol) and SiCl$_4$ (144 μL, 1.25 mmol) slowly at −78 °C. After 39 h, a solution of CH$_3$OH/Et$_3$N/CH$_2$Cl$_2$ (1/1/5, 5 mL) was added quickly at −78 °C. The resulting solution was vigorously stirred with a saturated aqueous NaHCO$_3$ solution (20 mL) at rt for 2 h. The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (20 mL × 3). The combined organic layers were dried over MgSO$_4$,
filtered, and concentrated in vacuo (5 mmHg). The residue was purified by column chromatography (SiO₂, 5% EtOAc/hexanes, KMnO₄) to give (−)-2.44 (165 mg, 33%, 3.4:96.6 er, Rᵣ = 0.7 in 10% EtOAc/hexanes) as a colorless oil and (+)-2.45 (367 mg, 65%, 71.4:28.6 er, Rᵣ = 0.5 in 10% EtOAc/hexanes) as pale yellow crystals. The enantiopurity of the recovered reactant (−)-2.44 was measured after ring-opening chlorinolysis to form (−)-2.45. Data for (−)-2.44: [α]D₂⁵ = −23.5 (c 1.74, CHCl₃); GC (B-DM, 30 psi, 180 °C) tᵣ 23.9 min (2.6%), 25.1 min (97.4%). Data for (+)-2.45: mp 34.0–36.0 °C; [α]D₂⁴ = +1.6 (c 2.01, CHCl₃); GC (B-DM, 30 psi, 180 °C) tᵣ 23.7 min (71.4%), 25.3 min (28.6%); ¹H NMR (600 MHz, CDCl₃) δ 6.07 (ddd, J = 17.1, 10.3, 7.4 Hz, 1H), 5.49 (dd, J = 16.1, 1.0 Hz, 1H), 5.35 (dd, J = 10.3, 0.8 Hz, 1H), 5.10 (dd, J = 7.4, 1.0 Hz, 1H), 4.56 (ddd, J = 9.0, 5.2, 1.4 Hz, 1H), 4.10 (dd, J = 9.4, 1.5 Hz, 1H), 4.05 (dd, J = 9.1, 1.1 Hz, 1H), 2.18 (d, J = 8.8 Hz, 1H), 2.00 (app dtd, J = 14.0, 10.0, 4.7 Hz, 1H), 1.80 (app ddt, J = 15.5, 10.7, 5.5 Hz, 1H), 1.58–1.51 (m, 1H), 1.45–1.38 (m, 1H), 1.36–1.24 (m, 10H), 0.89 (app t, J = 6.9 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 134.9, 119.5, 74.5, 64.7, 64.5, 61.7, 36.5, 32.0, 29.5, 29.3, 29.2, 26.7, 22.8, 14.3; IR (thin film) 3390, 2925, 2855, 933 cm⁻¹; HRMS (ESI-TOF) m/z calcd for C₁₄H₂₅Cl₄O [M + Cl]⁻ 349.0659, found 349.0665.

(+)-(11Z,13S,14S,15S,16S)-1-tert-Butyldimethylsiloxy-2,2,15,16-tetrachloro-13,14-epoxy-11-tetracosene (2.74): The solvents were bubbled with argon for 15 min before use. To a stirred solution of (−)-2.44 (134 mg, 0.481 mmol) and 2.67 (530 mg, 1.44 mmol) in DCE (480 µL) was added a solution of 2.50 (91.3 mg, 0.144 mmol) in CH₂Cl₂ (600 µL) in six portions (0, 15, 30, 45, 60, 75 min) at 35 °C while the reaction mixture was vigorously bubbled with argon (saturated with
After being stirred at 35 °C with argon bubbling for an additional 105 min, the reaction mixture was cooled to rt, filtered through a plug of silica gel (CH$_2$Cl$_2$, 10 mL), and concentrated in vacuo (5 mmHg). The residue was purified via column chromatography (140 mL of SiO$_2$, 5% CH$_2$Cl$_2$/hexanes, $R_f = 0.23$ in 10% CH$_2$Cl$_2$/hexanes) to give (+)-2.74 (57.1 mg, 19%, >20:1 = Z:E) as a colorless oil. Data for (+)-2.74: $[\alpha]_D^{25} = +0.088$ (c 2.65, CHCl$_3$); $^1$H NMR (499 MHz, CDCl$_3$) δ 5.86 (app td, $J = 8.9, 8.4$ Hz, 1H), 5.22 (app t, $J = 8.7$ Hz, 1H), 4.29–4.24 (m, 1H), 3.92 (s, 2H), 3.82–3.77 (m, 1H), 3.65 (d, $J = 8.9$ Hz, 1H), 3.52 (dd, $J = 8.0, 2.2$ Hz, 1H), 2.22 (app q, $J = 7.2$ Hz, 2H), 2.19–2.15 (m, 2H), 1.98–1.89 (m, 1H), 1.86–1.78 (m, 1H), 1.62–1.52 (m, 3H), 1.45–1.39 (m, 3H), 1.37–1.23 (m, 18H), 0.91 (s, 9H), 0.88 (app t, $J = 6.3$ Hz, 3H), 0.11 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 139.8, 121.6, 93.7, 72.3, 63.5, 31.3, 58.3, 54.0, 43.7, 35.9, 32.0, 29.5, 29.45, 29.43 (2C), 29.32, 29.28, 29.18, 29.12, 28.4, 26.5, 25.9, 24.9, 22.8, 18.4, 14.2, −5.2; IR (thin film) 2927, 2855, 1119, 939, 779 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for C$_{30}$H$_{56}$O$_2$SiNa [M + Na]$^+$ 639.2701, found 639.2719.

**Preparation of Alkene Cross Metathesis Partner for Danicalipin A and Malhamensilipin A**

**11-Dodecenal (2.64):**$^{47}$ To a flask containing magnesium (3.43 g, 141 mmol) in THF (10 mL) was added 1,2-dibromoethane (275 μL, 3.19 mmol) slowly. The mixture was allowed to sit at rt until gray precipitate formed. After dilution with additional THF (70 mL), a solution of 1-bromo-10-undecene (10.0 mL, 45.6 mmol) in THF (20 mL) was added over 1 h via a syringe pump. After being stirred for 1 h, the mixture was cooled to 0 °C and allowed to settle. The liquid phase was transferred via a cannula to a rapidly stirred solution of DMF (53 mL, 684 mmol) and THF (53 mL) at 0 °C. After being stirred for 20 min at rt, the reaction mixture was diluted with hexanes (200 mL)
and poured into 1 M aq HCl (200 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes (200 mL × 3). The combined organic extracts were washed with brine (100 mL), dried over MgSO₄, filtered, and concentrated in vacuo (5 mmHg). The residue was purified by column chromatography (300 mL of SiO₂, 5% EtOAc in hexanes) to afford 2.64 (6.33 g, 76%) as a colorless oil. Data for 2.64: ¹H NMR (500 MHz, CDCl₃) δ 9.76 (s, 1H), 5.81 (ddt, J = 17.0, 10.1, 6.7 Hz, 1H), 4.99 (dd, J = 17.0, 1.4 Hz, 1H), 4.92 (dd, J = 10.2, 0.8 Hz, 1H), 2.41 (td, J = 7.6, 1.7 Hz, 2H), 2.03 (app q, J = 7.1 Hz, 2H), 1.62 (tt, J = 7.3, 6.6 Hz, 2H), 1.39–1.35 (m, 2H), 1.33–1.25 (m, 10H); ¹³C NMR (126 MHz, CDCl₃) δ 203.0, 139.2, 114.1, 43.9, 33.8, 29.4, 29.34, 29.31, 29.13, 29.07, 28.9, 22.1; IR (thin film) 2926, 2854, 2715, 1727 cm⁻¹; HRMS (ESI-TOF) m/z calcd for C₁₂H₂₂ONa [M + Na]⁺ 205.1568, found 205.1561.

2,2-Dichloro-11-dodecenal (2.65):³ To a flask containing t-butylamine (634 μL, 6.03 mmol) was added 11-dodecenal (2.64) (1.00 g, 5.49 mmol) dropwise at 0 °C. After being stirred at rt for 45 min, the cloudy reaction mixture was dried over K₂CO₃ (3.79 g, 27.4 mmol), filtered, and concentrated in vacuo (25 mmHg). The residue was purified by bulb-to-bulb distillation under reduced pressure (0.25 mmHg, ABT 128–135 °C) to give the corresponding t-butylimine³ (1.21 g, ~92:8 imine:aldehyde) as a colorless oil. The t-butylimine was dissolved in CH₂Cl₂ (15 mL), and N-chlorosuccinimide (2.04 g, 15.3 mmol) was added at rt under air. After being stirred for 24 h, the reaction mixture was shaken with saturated aqueous Na₂S₂O₃ solution. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were washed with saturated aqueous NaCl solution, dried over Na₂SO₄, filtered, and concentrated in vacuo (25 mmHg). The residue was diluted with hexanes, filtered, and concentrated in vacuo (25
mmHg) to give the corresponding α,α-dichloro-τ-butylimine\(^3\) as a yellow oil (1.54 g, ~94:6 dichloride:monochloride). The crude material was dissolved in THF (10 mL), and 6 M aq HCl (10 mL) was added at rt. The biphasic mixture was stirred for 2 h prior to dilution with Et\(_2\)O. The organic layer was separated, and the aqueous layer was extracted with Et\(_2\)O. The combined organic extracts were washed with saturated aqueous NaHCO\(_3\) solution, dried over MgSO\(_4\), filtered, and concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO\(_2\), φ = 2.2 cm, l = 7 cm, n-pentane/CH\(_2\)Cl\(_2\), 2/1, \(R_f = \sim 0.20\), streaky, KMnO\(_4\)) and bulb-to-bulb distillation under reduced pressure (0.25 mmHg, ABT 129–135 °C) to give 2.65 (1.01 g, 73% over three steps, ~94% pure) as a colorless oil. Data for 2.65: \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 9.25 (s, 1H), 5.81 (ddt, \(J = 16.9, 10.2, 6.7\) Hz, 1H), 4.99 (dd, \(J = 17.1, 1.9\) Hz, 1H), 4.93 (dd, \(J = 10.2, 1.0\) Hz, 1H), 2.31–2.23 (m, 2H), 2.04 (dd, \(J = 14.4, 6.9\) Hz, 2H), 1.66–1.58 (m, 2H), 1.43–1.24 (m, 10H).

2,2-Dichloro-11-dodecen-1-ol (2.66): To a stirred solution of 2.65 (1.00 g, 3.98 mmol) in ethanol (12 mL) was added NaBH\(_4\) (151 mg, 3.98 mmol) at 0 °C under air. After being stirred for 30 min at rt, 1 M aq HCl (12 mL) was added. The cloudy mixture was diluted with H\(_2\)O and extracted with hexanes twice. The combined organic extracts were dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO\(_2\), φ = 2.2 cm, l = 13 cm, n-pentane/CH\(_2\)Cl\(_2\), 1/1, \(R_f = 0.29\), \(p\)-anisaldehyde) to give 2.66 (934 mg, 93%) as a colorless oil. Data for 2.66: \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 5.81 (ddt, \(J = 16.9, 10.2, 6.7\) Hz, 1H), 4.99 (dd, \(J = 17.1, 1.5\) Hz, 1H), 4.93 (d, \(J = 10.2\) Hz, 1H), 3.90 (d, \(J = 7.6\) Hz, 2H), 2.29 (t, \(J = 7.6\) Hz, 1H), 2.24–2.18 (m, 2H), 2.04 (dd, \(J = 14.3, 6.9\) Hz, 2H), 1.68–1.59 (m, 2H), 1.42–1.26 (m, 10H); \(^{13}\)C NMR
12-tert-Butyldimethysiloxy-11,11-dichloro-1-dodecene (2.67): To a stirred solution of 2.66 (348 mg, 1.37 mmol) and imidazole (187 mg, 2.75 mmol) in CH₂Cl₂ (2 mL) was added TBSCl (228 mg, 1.51 mmol) at rt. After being stirred for 48 h, the reaction mixture was diluted with CH₂Cl₂ (5 mL) and shaken with saturated aqueous NaHCO₃ (5 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes (10 mL × 3). The combined organic extracts were washed with saturated aqueous NaCl (3 mL), concentrated in vacuo (5 mmHg), and passed through a pad of silica gel (5% EtOAc in hexanes, 10 mL). The residue was purified by bulb-to-bulb distillation under reduced pressure (0.05 mmHg, ABT 170–180 °C) to afford 2.67 (453 mg, 90%) as a colorless oil.

Data for 2.67: ¹H NMR (500 MHz, CDCl₃) δ 5.81 (ddt, J = 17.0, 10.1, 6.7 Hz, 1H), 4.99 (dd, J = 17.3, 1.7 Hz, 1H), 4.93 (dd, J = 10.2, 1.0 Hz, 1H), 3.92 (s, 2H), 2.15–2.19 (m, 2H), 2.04 (app q, J = 7.2 Hz, 2H), 1.55–1.62 (m, 2H), 1.27–1.40 (m, 10H), 0.91 (s, 9H), 0.11 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 139.2, 114.1, 93.5, 72.1, 43.5, 33.8, 29.30, 29.29, 29.1, 29.0, 28.9, 25.7, 24.7, 18.3, −5.4; IR (thin film) 2928, 2856, 1118, 838 cm⁻¹; HRMS (CI-TOF) m/z calcd for C₁₈H₃₆Cl₂OSiNH₄ [M + NH₄]⁺ 384.2256, found 384.2257.
Synthesis of Mytilipin A

(±)-(2S,3R)-2,3-Dichloro-1-butanol (2.35): To a stirred solution of Et$_4$NCl (6.63 g, 40.0 mmol) and crotyl alcohol (1.44 g, 20.0 mmol, 19:1 = $E$/$Z$) in CH$_2$Cl$_2$ (60 mL) was bubbled Cl$_2$ at 0 °C until the reaction mixture turned yellow (ca. 1 min). Ethylene was bubbled until the yellow color disappeared (ca. 1 min). The resulting colorless solution was diluted with CH$_2$Cl$_2$ (50 mL) and shaken with a mixture of sat. aq. NaHCO$_3$ solution (50 mL) and sat. aq. Na$_2$S$_2$O$_3$ solution (50 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (50 mL). The combined organic extracts were shaken with sat. aq. NaCl solution (50 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (50 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo* (30 mmHg). The residue was purified by bulb-to-bulb distillation under reduced pressure (40 mmHg, ABT 120–130 °C) to afford (±)-2.35 (2.56 g, 89%, 19:1 dr) as a colorless oil. Data for (±)-2.35: bp 83–87 °C (30 mmHg, head temperature) $^{63}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 4.23 (dq, $J$ = 7.7, 6.7 Hz, 1 H), 4.05–3.99 (m, 3 H), 1.99 (bs, 1 H), 1.68 (d, $J$ = 6.6 Hz, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 67.8, 64.5, 56.2, 22.6; IR (thin film) 3390, 2986, 2938, 2883, 1455, 1382, 1196, 1072, 1017, 657 cm$^{-1}$; HRMS (CI) $m/z$ calcd for C$_4$H$_8$Cl$_2$ONH$_4$ [M + NH$_4$]$^+$ 160.0296, found 160.0289.
(±)-(2S,3R)-2,3-Dichlorobutanal (2.36): To a stirred suspension of (±)-2.35 (1.43 g, 10.0 mmol) and NaHCO$_3$ (2.52 g, 30.0 mmol) in CH$_2$Cl$_2$ (10 mL, saturated with H$_2$O) was added Dess–Martin periodinane (6.36 g, 15.0 mmol) slowly at 0 °C under air. After stirring for 10 min, the ice-bath was removed and the reaction mixture was stirred at rt for 30 min prior to the addition of n-pentane (100 mL). The resulting mixture was filtered, washed with ice cold sat. aq. NaHCO$_3$ (50 mL), dried over MgSO$_4$, and used directly for the next reaction without concentration. An analytical sample could be obtained upon concentration. $^1$H NMR (500 MHz, CDCl$_3$) δ 9.44 (d, $J = 3.1$ Hz, 1 H), 4.37 (dq, $J = 7.2$, 6.6 Hz, 1 H), 4.23 (dd, $J = 7.2$, 3.1, 1 H), 1.67 (d, $J = 6.6$, 3 H).

(±)-(3S,4S,5S,6R)-5,6-Dichloro-3,4-epoxy-1-heptene (2.38): To a stirred solution of TMP (3.71 mL, 22.0 mmol) in THF (50 mL) was added n-BuLi (2.35 M in hexanes, 8.94 mL, 21.0 mmol) at –78 °C. After stirring for 20 min, the LiTMP solution was cannulated into a solution of allyl bromide (1.82 mL, 21.0 mmol) and Et$_2$AlCl (1.0 M in hexanes, 40.0 mL, 40.0 mmol) in THF (100 mL) at –78 °C over 15 min. The resulting solution was stored at –78 °C while (±)-2.36 was prepared (see above). The solution of (±)-2.36 was cooled to –78 °C and cannulated over 1 h via a syringe needle fitted with a glass fiber filter. After stirring at –78 °C for 3 h, the reaction mixture was poured into an ice-cold 5 M aq. NaOH solution (200 mL). Et$_4$NCl (16.6 mg, 0.10 mmol) was added.$^{64,65}$ The biphasic mixture was vigorously stirred at rt for 1 h prior to the dilution with n-pentane (100 mL). The
organic layer was separated and the aqueous layer was extracted with \( n \)-pentane (200 mL). The combined organic extracts were washed with sat. aq. NH\(_4\)Cl solution (200 mL × 2) and H\(_2\)O (200 mL × 5), dried over Na\(_2\)SO\(_4\), filtered, and concentrated \textit{in vacuo} (200 mmHg). The residue was purified by column chromatography (SiO\(_2\), \( n \)-pentane/CH\(_2\)Cl\(_2\), 1/0 to 8/1, \( R_f = 0.22 \) in 8/1, \( p \)-anisaldehyde) and concentrated at 200 mmHg. The resulting colorless oil was purified by bulb-to-bulb distillation under reduced pressure (40 mmHg, ABT 125–135 °C) to give (±)-2.38 (941 mg, 52%, 98:2 \( dr \)) as a colorless oil. Data for (±)-2.38: bp 79–81 °C (30 mmHg, head temperature)\(^{63}\); \( ^1 \)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.81 (ddd, \( J = 17.1, 10.6, 5.7 \) Hz, 1 H), 5.52 (d, \( J = 17.1 \) Hz, 1 H), 5.46 (d, \( J = 10.7 \) Hz, 1 H), 4.38 (qd, \( J = 6.7, 4.4 \) Hz, 1 H), 3.72 (dd, \( J = 9.1, 4.2 \) Hz, 1 H), 3.58 (dd, \( J = 5.2, 4.7 \) Hz, 1 H), 3.38 (dd, \( J = 9.1, 4.3 \) Hz, 1 H), 1.68 (d, \( J = 6.8 \) Hz, 3 H); \( ^{13} \)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 130.2, 121.4, 61.6, 58.9, 57.9, 56.0, 21.0; IR (thin film) 3092, 2983, 2935, 1868, 1641, 1447, 1406, 1382, 1280, 1248, 1209, 1060, 982, 934, 919, 895, 840, 824, 805, 781, 757, 707, 668, 647, 597, 561 cm\(^{-1}\); HRMS (CI) \( m/z \) calcd for C\(_7\)H\(_{10}\)Cl\(_2\)ONH\(_4\) [M + NH\(_4\)]\(^+\) 198.0452, found 198.0460.

8-Nonenal (S1): Magnesium (3.74 g, 154 mmol) was flame-dried in a 250 mL round bottom flask. THF (10 mL) was added followed by 1,2-dibromoethane (310 \( \mu \)L, 3.59 mmol). The flask was heated intermittently with a heat gun in order to activate the magnesium. After formation of a grey solid and bubbling were observed, THF (90 mL) was added. A solution of 8-bromo-1-octene (9.81 g, 51.3 mmol) in THF (10 mL) was added via syringe pump over 1 h. After stirring for 30 min, the mixture was cooled to –15 °C and cannulated to a solution of THF (100 mL) and DMF (56 mL) at –15 °C. The cloudy suspension was warmed up to room temperature and stirred for 1 h. The reaction mixture
was diluted with *n*-pentane (250 mL) and poured into 0.5 M aq. HCl (200 mL). The biphasic mixture was extracted three times with *n*-pentane (100 mL) and concentrated *in vacuo*. The residue was purified by column chromatography (600 mL SiO$_2$, 3% EtOAc in hexanes) to afford 8-nonenal (4.69 g, 65%) as a colorless oil. Data for 8-nonenal: bp 39–43 °C (0.05 mmHg, head temperature); $^1$H NMR (600 MHz, CDCl$_3$) δ 9.76 (s, 1 H), 5.80 (ddt, $J = 17.0, 10.2, 6.7$ Hz, 1 H), 4.99 (dd, $J = 17.1, 1.5$ Hz, 1 H), 4.94 (dd, $J = 10.2, 0.8$ Hz, 1 H), 2.42 (td, $J = 7.3, 1.6$ Hz, 2 H), 2.04 (dt, $J = 7.0, 7.0$ Hz, 2 H), 1.63 (tt, $J = 7.3, 7.1$ Hz, 2 H), 1.41–1.29 (m, 6 H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 202.9, 138.9, 114.3, 43.9, 33.7, 29.0, 28.8, 28.6, 22.0; IR (thin film) 3076, 2928, 2855, 1709, 1640, 1459, 1413, 1288, 994, 910 cm$^{-1}$; HRMS (Cl) $m/z$ calcd for C$_9$H$_{16}$ONH$_4$ [M + NH$_4]^+$ 158.1545, found 158.1551.

(E)-1-Chloro-1,9-decadiene (2.72): To a stirred suspension of CrCl$_2$ (3.69 g, 30.0 mmol) in THF (23 mL) at 60 °C was added CHCl$_3$ (1.20 mL, 15.0 mmol) at once. After 1 min, a solution of 8-nonenal (1.40 g, 10.0 mmol) in THF (10 mL) was added. The green solution turned deep purple. After 3 h, the oil bath was removed and, once the mixture had cooled, *n*-pentane (50 mL) and water (100 mL) were added. The biphasic mixture was separated and the aqueous phase was extracted three times with *n*-pentane. The combined organic extracts were dried over MgSO$_4$, filtered and concentrated *in vacuo* (20 °C, >50 mmHg). The residue was purified by column chromatography (200 mL SiO$_2$, *n*-pentane, $R_f = 0.7$) to afford 2.72 (1.36 g, 79%, 93:7 = E:Z) as a colorless oil. Data for 2.72: bp 55 °C (5 mmHg, head temperature); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.94–5.86 (m, 2 H), 5.84–5.75 (m, 1 H), 4.99 (dd, $J = 17.1, 1.3$ Hz, 1 H), 4.94 (dd, $J = 10.2, 0.8$ Hz, 1 H), 2.06–2.02 (m, 4 H), 1.38–1.29 (m, 8 H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 139.1, 134.1, 116.6, 114.2, 33.7, 30.8,
29.0, 28.80 (2C), 28.79; IR (thin film) 3075, 2928, 2855, 1640, 994, 933, 910, 804 cm\(^{-1}\);

HRMS (Cl) \(m/z\) calcd for C\(_{10}\)H\(_{17}\)Cl \([M]^+\) 172.1019, found 172.1021.

\((\pm)-(2R,3S,4S,5S,6Z,14E)-2,3,15\)-Trichloro-4,5-epoxy-6,14-pentadecadiene (2.73): All the reactants and solvents except for C633 were bubbled with argon for 10 min. To a stirred solution of \((\pm)-2.38\) (45 mg, 0.25 mmol) and 2.72 (130 mg, 0.75 mmol) in DCE (250 \(\mu\)L) in a test tube (12 mm \(\times\) 75 mm) was added a solution of C633 (47.5 mg, 0.075 mmol) in CH\(_2\)Cl\(_2\) (250 \(\mu\)L) in three portions (0, 0.5, 1.0 h) at 35 °C while the reaction mixture was vigorously bubbled with argon (saturated with DCE)\(^{58}\). After stirring at 35 °C with argon bubbling for an additional 2 h, the reaction mixture was cooled to rt, filtered through silica gel (CH\(_2\)Cl\(_2\), 50 mL), and concentrated \textit{in vacuo} (30 mmHg). The residue was purified by column chromatography (SiO\(_2\), \(n\)-pentane/CH\(_2\)Cl\(_2\), 1/0 to 4/1, \(R_f = 0.27\) in 4/1, \(p\)-anisaldehyde) to give \((\pm)-2.73\) (26 mg, 32%, \(>20:1 = Z:E\)) as a colorless oil. Data for \((\pm)-2.73\): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.95–5.84 (m, 3 H), 5.25–5.21 (m, 1 H), 4.39 (qd, \(J = 6.6, 4.2\) Hz, 1 H), 3.75 (dd, \(J = 8.6, 4.1\) Hz, 1 H), 3.73 (dd, \(J = 9.6, 4.0\) Hz, 1 H), 3.36 (dd, \(J = 9.2, 4.2\) Hz, 1 H), 2.23–2.20 (m, 2 H), 2.07–2.02 (m, 2 H), 1.67 (d, \(J = 6.7\) Hz, 3 H), 1.44–1.25 (m, 8 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 139.6, 134.0, 121.5, 116.7, 62.5, 58.9, 57.6, 52.7, 30.8, 29.2, 28.9, 28.8 (2C), 28.1, 20.8; IR (thin film) 3063, 2981, 2929, 2855, 1731, 1634, 1455, 1382, 1285, 1251, 935, 920, 896, 799, 766, 745, 682, 648 cm\(^{-1}\); HRMS (Cl) \(m/z\) calcd for C\(_{15}\)H\(_{23}\)Cl\(_3\)ONH\(_4\) \([M + NH_4]^+\) 342.1158, found 342.1161. Data for (+)-2.73: \([\alpha]_D^{25}\) = +2.0 (c = 0.50, CHCl\(_3\))\(^{66}\).
(±)-(2R,3S,4S,5R,6Z,14E)-2,3,5,15-Tetrachloropentadeca-6,14-dien-4-ol (2.82): To a stirred solution of (±)-2.73 (49 mg, 0.15 mmol) and Et₄NCl (75 mg, 0.45 mmol) in CH₂Cl₂ (0.6 mL) was added BF₃·OEt₂ (37 μL, 0.30 mmol) at −78 ºC. After stirring for 1 h, the reaction mixture was poured into ice-cold sat. aq. NaHCO₃ solution (10 mL). To the biphasic mixture were added CH₂Cl₂ (10 mL) and H₂O (10 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (10 mL × 2). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo (30 mmHg). The residue was purified by column chromatography (SiO₂, n-pentane/CH₂Cl₂, 4/1 to 2/1, Rf = 0.22 in 2/1, p-anisaldehyde) to give (±)-2.82 (39 mg, 72%, >20:1 dr) as a colorless oil. Data for (±)-2.82: ¹H NMR (500 MHz, CDCl₃) δ 5.95–5.86 (m, 2 H), 5.73 (dd, J = 10.6, 9.9 Hz, 1 H), 5.66 (ddd, J = 10.6, 7.5, 7.5 Hz, 1 H), 5.39 (d, J = 9.9 Hz, 1 H), 4.69 (qd, J = 6.5, 3.0 Hz, 1 H), 4.27 (dd, J = 9.2, 3.0 Hz, 1 H), 3.68 (dd, J = 10.7, 9.3 Hz, 1 H), 2.32 (d, J = 10.7 Hz, 1 H), 2.22–2.08 (m, 2 H), 2.07–2.03 (m, 2 H), 1.57 (d, J = 6.6 Hz, 3 H), 1.40–1.25 (m, 8 H); ¹³C NMR (126 MHz, CDCl₃) δ 135.6, 133.9, 125.9, 116.7, 75.2, 67.1, 59.9, 56.2, 30.8, 28.9, 28.9, 28.74, 28.70, 27.6, 19.0; IR (thin film) 3530, 2930, 2856, 1635, 1456, 1381, 1266, 1092, 934, 796 cm⁻¹. Data for (–)-2.82: [α]D²⁵ = −95.7 (c = 0.32, CHCl₃).

(±)-(2R,3S,4R,5S,6S,7R,E)-2,3,5,6,7,15-Hexachloropentadeca-14-en-4-ol (2.83): To a stirred solution of (±)-2.82 (60 mg, 0.17 mmol) in CH₂Cl₂ (1.5 mL) was added a solution of Et₄NCl₃ (59
mg, 0.25 mmol) in CH₂Cl₂ (0.2 mL) at –78 °C. After stirring for 5 min, the reaction mixture was bubbled with ethylene until the yellow color disappeared. The mixture was diluted with CH₂Cl₂ (5 mL) and shaken with sat. aq. NaHCO₃ solution (5 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (5 mL × 2). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo (30 mmHg). The residue (93:7 dr) was purified by column chromatography (SiO₂, n-pentane/CH₂Cl₂, 2/1, Rf = 0.24, CAM) to give (±)-2.83 (62 mg, 86%, 97:3 dr) as a colorless oil which slowly crystallized on standing, as well as a less diastereomERICally enriched fraction (6 mg, 8%, 71:29 dr). Data for (±)-2.83: ¹H NMR (500 MHz, CDCl₃) δ 5.95–5.85 (m, 2 H), 4.85 (d, J = 8.3 Hz, 1 H), 4.67 (qd, J = 6.6, 2.6 Hz, 1 H), 4.31 (dd, J = 9.6, 2.7 Hz, 1 H), 4.26 (dd, J = 8.3, 2.3 Hz, 1 H), 4.19 (ddd, J = 8.0, 5.3, 2.3 Hz, 1 H), 4.02 (dd, J = 11.2, 10.1 Hz, 1 H), 2.29 (d, J = 11.7 Hz, 1 H), 2.07–2.03 (m, 2 H), 1.99–1.93 (m, 1 H), 1.92–1.86 (m, 1 H), 1.61 (d, J = 6.6 Hz, 3 H), 1.55–1.50 (m, 1 H), 1.41–1.25 (m, 7 H); ¹³C NMR (126 MHz, CDCl₃) δ 133.8, 116.9, 72.0, 67.7, 67.5, 66.4, 61.2, 56.1, 36.4, 30.8, 28.69, 28.65 (2C), 26.2, 19.1; IR (thin film) 3534, 2930, 2856, 1632, 1462, 1455, 1382, 1331, 1267, 1188, 1090, 1058, 1012, 935, 805, 777, 702 cm⁻¹.; HRMS (CI) m/z calcd for C₁₅H₂₄Cl₁₆ONH₄ [M + NH₄]⁺ 450.0273, found 450.0277. Data for (–)-2.83: [α]D25 = –21.7 (c = 0.28, CHCl₃)66 (lit. [α]D25 +27.4 (c = 0.42, CHCl₃) for (+)-2.83ɜ). The analytical data for 2.83 were in agreement with literature precedent.²⁷

(±)-(2R,3S,4R,5S,6S,7R,E)-2,3,5,6,7,15-Hexachloropentadec-14-en-4-yl hydrogen sulfate (1.3)²⁷: To a stirred solution of (±)-2.83 (37 mg, 0.085 mmol) in THF (1.7 mL) was added SO₃·py (41 mg, 0.26 mmol) at rt under air. After 30 min, the heterogeneous reaction mixture was diluted with
CH₂Cl₂ (8 mL), filtered, and concentrated *in vacuo* (30 mmHg). The residue was purified by column chromatography twice (SiO₂, CH₂Cl₂/MeOH, 9/1, Rf = 0.17, KMnO₄) to give (±)-1.3 (41 mg, 94%) as a colorless film. Data for (±)-1.3: ¹H NMR (600 MHz, acetone-d₆) δ 6.12 (ddd, J = 13.2, 1.4, 1.4, 1 H), 5.94 (ddd, J = 13.2, 7.4, 7.4, 1 H), 5.09 (ddd, J = 8.8, 4.2, 1.7 Hz, 1 H), 5.02 (qd, J = 6.4, 1.8 Hz, 1 H), 4.80 (dd, J = 9.8, 1.0 Hz, 1 H), 4.70 (dd, J = 9.8, 1.0 Hz, 1 H), 4.69 (dd, J = 9.8, 1.8 Hz, 1 H), 4.43 (dd, J = 9.9, 1.8 Hz, 1 H), 2.11–2.07 (m, 2 H), 1.94–1.88 (m, 1 H), 1.86–1.81 (m, 1 H), 1.60 (d, J = 6.4 Hz, 3 H), 1.58–1.55 (m, 1 H), 1.44–1.29 (m, 7 H); ¹³C NMR (126 MHz, acetone-d₆) δ 135.2, 117.5, 75.7, 69.1, 68.8, 67.9, 63.2, 57.2, 37.8, 31.3, 29.52, 29.49, 29.3, 26.7, 19.3. Data for (–)-1.3: [α]D²⁵ = −33.3 (c = 0.30, MeOH)° (lit. [α]D²⁴ +49.0 (c = 0.59, MeOH) for (+)-1.3). The analytical data for 1.3 were in agreement with the data given from the isolation paper.°

(+)-(3R,4R,5R,6S)-5,6-Dichloro-3,4-epoxy-1-heptene (2.38), (+)-(3R,4S,5S,6R)-3,5,6-trichloro-1-hepten-4-ol (2.39): To a stirred solution of (±)-2.38 (98 mg, 0.54 mmol) and R,R-dimeric Denmark catalyst (91 mg, 0.11 mmol) in CH₂Cl₂ (5.4 mL) were added iPr₂NEt (9 μL, 0.054 mmol) and SiCl₄ (62 μL, 0.54 mmol) at −78 °C. After stirring for 72 h, a solution of CH₃OH/Et₃N/CH₂Cl₂ (1/1/5, 4 mL) was added quickly at −78 °C. The resulting solution was vigorously stirred with a sat. aq. NaHCO₃ solution (20 mL) at rt for 2 h and filtered. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (10 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo* (200 mmHg). The residue was purified by column chromatography (SiO₂, n-pentane/CH₂Cl₂, 1/1, p-anisaldehyde) and concentrated at 200 mmHg to give (+)-2.38 (42 mg, 43%, Rf = 0.68, 93.5:6.5 er) as a colorless oil and (+)-2.39 (55 mg, 47%, Rf =
0.29, 17.0:83.0 er) as white crystals. \( R,R \)-Dimeric Denmark catalyst was recovered by flushing the column (\( \text{CH}_2\text{Cl}_2/\text{PrOH}, 10/1, R_f = 0.37, \text{UV} \)). Data for (+)-2.38: [\( \alpha \)]\( _D \)\( ^{25} \) = +86.5 (c = 1.43, CHCl\( _3 \)); GC (B-DM, 30 psi, 115 °C) \( t_R \) 6.5 min (93.5%), 6.7 min (6.5%). Data for (+)-2.39: [\( \alpha \)]\( _D \)\( ^{25} \) = +39.1 (c = 2.20, CHCl\( _3 \)); GC (B-DM, 30 psi, 160 °C) \( t_R \) 4.8 min (17.0%), 5.0 min (83.0%); \(^1\text{H} \) NMR (500 MHz, CDCl\( _3 \)) \( \delta \) 6.03 (ddd, \( J \) = 16.9, 10.2, 7.6 Hz, 1 H), 5.49 (d, \( J \) = 16.9 Hz, 1 H), 5.35 (d, \( J \) = 10.2 Hz, 1 H), 5.08 (d, \( J \) = 7.6 Hz, 1 H), 4.71 (qd, \( J \) = 6.6, 2.8 Hz, 1 H), 4.29 (dd, \( J \) = 9.5, 2.7 Hz, 1 H), 3.76 (ddd, \( J \) = 9.9, 9.9, 1.4 Hz, 1 H), 2.24 (d, \( J \) = 10.0 Hz, 1 H), 1.58 (d, \( J \) = 6.6 Hz, 3 H); \(^{13}\text{C} \) NMR (126 MHz, CDCl\( _3 \)) \( \delta \) 134.4, 119.7, 74.7, 66.8, 64.9, 56.3, 18.8; IR (thin film) 3533, 3089, 2983, 2935, 1646, 1447, 1382, 1331, 1269, 1254, 1191, 1092, 1057, 1016, 988, 937, 913, 887, 784, 711, 666, 562, 486 cm\(^{-1} \); HRMS (CI) \( m/z \) calcld for \( \text{C}_7\text{H}_11\text{Cl}_3\text{ONH}_4 \) [M + \( \text{NH}_4 \)]\(^+ \) 234.0219, found 234.0222. (+)-2.38 (92.5:7.5 er) was carried through the identical sequence described above to afford (−)-mytilipin A. Optical rotation data for each enantioenriched intermediate can be found above.

**Other Experimentals**

[Diagram of heptachloro alcohol 2.87a]

**heptachloro alcohol 2.87a:** A vial was charged with Z-alkene 2.79 (4.7 mg, 7.50 \( \mu \)mol) and DCM (100 \( \mu \)L) and cooled to −78 °C. Et\( _4 \)NCl (115 \( \mu \)L of a 23.5 mg/mL solution in DCM, 1.5 equiv) via syringe and the mixture was allowed to stir for 1 hour. The cooling bath was removed and a 1/1 solution of sat. aq. NaHCO\( _3/\text{Na}_2\text{S}_2\text{O}_3 \) (1 mL) was added at once and the biphasic mixture was extracted with hexanes (3 × 1 mL). The combined organics were dried with MgSO\( _4 \), concentrated \textit{in vacuo} and purified via column chromatography (SiO\( _2 \), 10% EtOAc/Hexanes, \( R_f = 0.39 \)) to provide
**heptachloro alcohol S2**: A vial was charged with Z-alkene **2.79** (5.4 mg, 7.72 μmol) and DCM (100 μL) and cooled to −78 °C. Et₄NCl₃ (115 μL of a 23.5 mg/mL solution in DCM, 1.5 equiv) via syringe and the mixture was allowed to stir for 1 hour. The cooling bath was removed and a 1/1 solution of sat. aq. NaHCO₃/Na₂S₂O₃ (1 mL) was added at once and the biphasic mixture was extracted with hexanes (3 × 1 mL). The combined organics were dried with MgSO₄, concentrated *in vacuo*. The oil was taken in MeOH (1 mL) and CSA (2 mg) was added. The mixture was allowed to stand for 20 minutes, then sat. aq. NaHCO₃ (1 mL) was added and the aqueous phase was extracted with hexanes (3 × 1mL), dried with MgSO₄, and concentrated *in vacuo*. The oil was purified via column chromatography (SiO₂, 10% EtOAc/Hexanes, Rf = 0.39) to provide S2 (5.0 mg, 96% yield, 80:20 dr) as an oil. ¹H NMR (500 MHz, CDCl₃) δ 4.83 (d, J = 10.0, 1H), 4.55 (t, J = 6.2, 1H), 4.47–4.50 (m, 2H), 4.32 (d, J = 9.0, 1H), 4.26 (d, J = 10.6, 1H), 3.92 (s, 3H), 2.15–2.19 (m, 2H), 1.98–2.06 (m, 1H), 1.88–1.97 (m, 1H), 1.78–1.85 (m, 2H), 1.52–1.67 (m, 6H), 1.27–1.43 (m, 14H), 0.91 (s, 9H), 0.90 (t, J = 6.3, 3H), 0.11 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 93.6, 72.3, 71.6, 66.0,
Z-allylic alcohol 2.56: A vial is charged with adamantyl catalyst 2.50 (9.5 mg, 0.10 equiv) in a glovebox, sealed and removed from the glovebox and fitted with a balloon of argon. The vial is placed in a 35 °C oil bath and a degassed solution of DCE (100 μL), 1-decene (138 μL, 5 equiv), and allylic bromide 2.54 (prepared by the same method as 2.44 with omission of the basic workup) (52.6 mg, 0.146 mmol) is added to the vial via syringe. After stirring for 1.5 hours the reaction is concentrated and purified via column chromatography (10 mL SiO₂, 1% EtOAc/Hexanes, R_f = 0.42 in 10% EtOAc/Hexanes) to provide 2.56 (9.0 mg, 10% yield) and ca. 85% recovered starting material. 

**1H NMR (500 MHz, CDCl₃)** δ 7.14 (t, J = 7.6, 1H), 7.10 (d, J = 6.9, 1H), 6.83–6.86 (m, 2H), 5.88 (dt, J = 15.3, 7.1, 1H), 5.54 (dd, J = 15.4, 7.2, 1H), 4.52–4.57 (m, 1H), 4.45–4.48 (m, 1H), 4.28–4.33 (m, 1H), 3.79 (dd, J = 8.2, 2.0, 1H), 2.68–2.72 (m, 2H), 2.35–2.40 (m, 2H), 1.89–1.97 (m, 1H), 1.86 (d, J = 4.3, 1H), 1.73–1.80 (m, 1H), 1.48–1.53 (m, 2H), 1.37–1.42 (m, 2H), 1.37 (d, J = 6.1, 6H), 1.24–1.32 (m, 8H), 0.88 (t, J = 6.4, 3H); **13C NMR (126 MHz, CDCl₃)** δ 155.9, 136.0, 131.0, 130.4, 129.2, 127.2, 120.2, 113.0, 73.8, 69.9, 67.2, 62.0, 36.3, 32.6, 32.0, 30.3, 29.5, 29.3, 29.2, 26.6, 22.8, 22.4, 14.3; IR (thin film) 2957, 2922, 2851, 1458, 1240 cm⁻¹; HRMS (ESI) m/z calcd for C₂₄H₃₈Cl₂O₂Na [M + Na]⁺ 451.2147, found 451.2141.
2.6 References


(55) At the initial stage of optimization, a catalytic amount of Et₄NCl was employed as an indicator of the completion of the reaction. After all the alkene substrate is consumed, Et₄NCl₃ is formed with an excess of Cl₂ and shows deep yellow color as a sign of.

(56) An NMR sample of crude (±)-**2.16** showed no noticeable further decomposition after standing at rt overnight.

(57) Although the epoxide formation can proceed without a phase transfer catalyst, the addition of a catalytic amount of Et₄NCl facilitates the epoxide formation and ensures complete conversion.

(58) The vinyl epoxide decomposed significantly during reactions without argon bubbling.
(59) In the presence of an excess of n-Bu₃SnH, dechlorination of one of the gem-dichlorides was often observed.


(63) The boiling point was measured by short path distillation.


(66) The enantioenriched sample was prepared from kinetically resolved (+)-2.38 (92.5:7.5 er).

(67) The crude material contained ca. 20% of S₂N₂’ products.

PART II  PROGRESS TOWARDS THE SYNTHESIS OF THE PSAMMAPLYSIN FAMILY OF NATURAL PRODUCTS

Chapter 3: Bromotyrosine Derived Natural Products as Targets for Synthesis

3.1 Isolation and Biological Activity of Psammaplysins

The psammaplysin family of natural products have been known since the 1980’s. In the course of their isolation there have been sporadic reports of the biological activity of the psammaplysins including antimalarial, anti-HIV, antibiotic (including activity for two strains of methicillin resistant *Staphylococcus aureus*), and antitumor activity. The psammaplysin’s antibiotic activity is postulated to uniquely disrupt prokaryotic cell division by inhibiting equal partitioning of DNA into the daughter cells, which is important given the emerging problem of antibacterial resistance.

Studies on the secondary metabolites isolated from (order Verongida) *Psammaplysilla purpurea* collected from the Gulf of Eilat by Kashman and co-workers revealed two novel brominated natural products which they named psammaplysin A and B. At the time, multiple bromotyrosine derived natural products from the Verongida order of sponges had already been isolated and well-characterized, such as aerothionin (3.1) and fistularin-3 (3.2) (Figure 3.1a). Because the spectroscopic data of psammaplysin A and B closely resembled the 5,6-spiroyclic ring moiety present in the aerothionins and fistularins, Kashman and co-workers incorrectly assigned psammaplysin A and B as the structures 3.3 and 3.4, respectively (Figure 3.1b). In 1985, three years after Kashman’s original communication, Clardy reisolated and refined the structure of psammaplysin A (3.5) and B (3.6) using NMR and X-ray diffraction studies to the currently accepted structures possessing the novel spirooxepin-isoxazoline ring fusion. Although Clardy was able to
determine the relative stereochemistry of psammaplysin A (3.5) using X-ray diffraction, the data was not refined enough to determine the absolute stereochemistry. However, the absolute configuration has been assigned with confidence by comparison of ECD spectra of the psammaplysin with the ECD spectra of aerothionin 3.1, for which the absolute configuration is known.²

Figure 3.1 a. Other bromotyrosine derived natural products b. Original incorrect assignment of psammaplysin structure and the revised structure

![Diagram of psammaplysin structure]

The spirooxepin-isoxazoline ring system is the most striking structural feature of the psammaplysin. All natural products in the psammaplysin family possess this structural motif; members within the family differ only by the functionality of the bromotyrosine side chain at two positions, with a few exceptions (psammaplysin I–K (3.19–3.21)). The substitution at C19 is invariably a hydrogen or hydroxyl; on the basis of HPLC and Mosher ester analysis the compounds containing a hydroxyl at C19 are a mixture of diastereomers.² The functionality at C20 is invariably a free or substituted amine. The spirooxepin-isoxazoline ring system has been shown to be critical for cytotoxic activity;
the side chains of psammaplysin A and B alone 3.7–3.10 (also isolated natural products) show no cytotoxicity (Figure 3.2). However, the bromotyrosine side chain does play a role in modulating the biological activity of the psammaplysins.

**Figure 3.2** The side chain of psammaplysin A and B shows no cytotoxicity

When Scheuer first disclosed the structures of psammaplysins D (3.12) and E (3.14) in 1993 the only other psammaplysins reported at the time were A–C (3.5, 3.6, 3.11). Scheuer reported cytotoxic activity for psammaplysin E against human KB (oral epidermoid carcinoma) and human LoVo (colon adenocarcinoma) cells at 5 μg/mL as well as modest immunosuppressive activity. Psammaplysin D demonstrated activity against the Haitian RF strain of human immunodeficiency virus (HIV) (51% inhibition at 0.1 μg/mL). In 2013, after many new members of the psammaplysin family had been isolated, Lee and co-workers confirmed the poor cytotoxicity of psammaplysin D (GI₅₀ 21-27 μM) compared to psammaplysins A, B, E and X against several human tumor cell lines (GI₅₀ ca. 0.5-4 μM). The poor cytotoxicity of psammaplysin D was attributed to the lipophilic side chain, the only structural difference between it and the other cytotoxic members in the family (Table 3.1).
Table 3.1 The structure and biological activity of the psammaplysin family of natural products. NR = none reported

<table>
<thead>
<tr>
<th>Psammaplysin</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Biological activity</th>
</tr>
</thead>
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<tr>
<td>3.5 A</td>
<td>H</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>antibiotic&lt;sup&gt;6,11&lt;/sup&gt;, cytotoxic&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>3.6 B</td>
<td>OH</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>antibiotic&lt;sup&gt;6,11&lt;/sup&gt;, cytotoxic&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>3.11 C</td>
<td>OH</td>
<td>NHMe</td>
<td>cytotoxic&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>OH</td>
<td></td>
<td>anti-HIV&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>3.13 N</td>
<td>H</td>
<td></td>
<td>NR&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>3.14 E</td>
<td>H</td>
<td></td>
<td>cytotoxic&lt;sup&gt;1,7&lt;/sup&gt;</td>
</tr>
<tr>
<td>3.15 19-hydroxy E</td>
<td>OH</td>
<td></td>
<td>antimalarial&lt;sup&gt;2&lt;/sup&gt;, cytotoxic&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>3.16 F</td>
<td>H</td>
<td>NHMe</td>
<td>antimalarial&lt;sup&gt;10&lt;/sup&gt;, antibiotic (MRSA)&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>3.17 G</td>
<td>H</td>
<td>NMeCONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>antimalarial&lt;sup&gt;10&lt;/sup&gt;</td>
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<tr>
<td>3.18 H</td>
<td>H</td>
<td>N&lt;sup&gt;+&lt;/sup&gt;Me&lt;sub&gt;3&lt;/sub&gt;</td>
<td>antimalarial&lt;sup&gt;9&lt;/sup&gt;, antibiotic (MRSA)&lt;sup&gt;8&lt;/sup&gt;</td>
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<tr>
<td>3.19 I</td>
<td>14-desbromo-psammaplysin A</td>
<td></td>
<td>NR&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>3.20 J</td>
<td>14-desbromo-psammaplysin B</td>
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<td>NR&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>3.21 K</td>
<td>C19 aldehyde</td>
<td></td>
<td>NR&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>3.22 K dimethoxy acetal</td>
<td>C19 dimethoxy acetal</td>
<td></td>
<td>NR&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>3.23 L</td>
<td>R&lt;sup&gt;1&lt;/sup&gt; = OCONH = R&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>NR&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>3.24 M</td>
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<td>n = 16</td>
<td>OH</td>
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<td>n = 12</td>
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<td>NR&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>n = 12</td>
<td>OH</td>
<td>NR&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
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<td>n = 11</td>
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<td>NR&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>H</td>
<td>NR&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>3.32 19-hydroxy S</td>
<td>n = 12</td>
<td>OH</td>
<td>NR&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>3.33 T</td>
<td>n = 14</td>
<td>H</td>
<td>NR&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>3.34 19-hydroxy T</td>
<td>n = 14</td>
<td>OH</td>
<td>NR&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>3.35 U</td>
<td>n = 8, m = 3</td>
<td>H</td>
<td>NR²</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
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<td>-----</td>
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<tr>
<td>3.36</td>
<td>19-hydroxy U</td>
<td>n = 8, m = 3</td>
<td>OH</td>
</tr>
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<td>3.37</td>
<td>V</td>
<td>n = 8, m = 4</td>
<td>H</td>
</tr>
<tr>
<td>3.38</td>
<td>W</td>
<td>n = 11, m = 4</td>
<td>H</td>
</tr>
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<td>3.39</td>
<td>19-hydroxy W</td>
<td>n = 11, m = 4</td>
<td>OH</td>
</tr>
<tr>
<td>3.40</td>
<td>X</td>
<td>X = Cl</td>
<td>H</td>
</tr>
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<td>3.41</td>
<td>19-hydroxy X</td>
<td>X = Cl</td>
<td>OH</td>
</tr>
<tr>
<td>3.42</td>
<td>Y</td>
<td>X = H</td>
<td>H</td>
</tr>
</tbody>
</table>

It has been demonstrated that psammaplysin H (3.18) is a more potent antimalarial (IC₅₀ 0.41 μM) than psammaplysins F (3.16) (IC₅₀ 1.92 μM) and G (3.18) (IC₅₀ 5.22 μM) when tested against the chloroquine-sensitive malarial parasite *Plasmodium falciparum*.⁹ However, when tested against Gram-positive bacteria psammaplysin F and H both inhibit bacterial growth by 80% or greater at 50 μM. Methicillin-resistant *Staphylococcus aureas* (MRSA) is a Gram-positive bacteria that has left healthcare providers at the mercy of a limited arsenal of antibiotics such as vancomycin—often a drug of last resort.¹⁴,¹⁵ When treated with psammaplysins F, MRSA daughter cells form with extra or missing chromosomes. It is suggested that the amine functionality of R² on psammaplysin F increases cell membrane permeability on Gram-positive bacteria, increasing potency. Alternatively, psammaplysin H alters the morphology of MRSA, causing structural changes such as plasma membrane blebbing. This result indicates the possibility of inhibition of cell division or DNA damage.⁸

Synthesis has the ability to access the psammaplysins and derivatives thereof, which would allow for a more thorough analysis of the psammaplysins’ biological activity. The ideal synthesis would allow rapid access to the spirooxepin-isoxazoline core with flexibility for the installation of different side chains to further probe the structure-activity relationship.
3.2 Biosyntheses of Bromotyrosine Derived Natural Products

The psammaplysins are structurally related to other bromotyrosine derived natural products such as the psammaplin, aerothyonin, bastadin, fistularin and lipopurealin family,\textsuperscript{16,17} all of which were isolated from the \textit{Verongida} order of marine sponges. The structural similarities are due to the similar biosynthetic conversion of tyrosine into a brominated \(\alpha\)-oximinoamide secondary metabolite. However, the psammaplysin family is unique in that it possesses a spirooxepin-isoxazoline ring system.

In a mechanism put forth by Lindel,\textsuperscript{17} the biosynthesis of the core structure of psammaplysin and other \(\alpha\)-oximinoamide derived natural products are interrelated, likely starting from \(\alpha\)-oximinoamide \textbf{3.43}, which is also the core of the psammaplin and lipopurealin families of natural products. Methylation and oxidation of \textbf{3.43} would provide arene oxide \textbf{3.44}, which has never been isolated (Scheme 3.1). Fragmentation of the high-energy arene oxide could proceed by oxime-mediated opening to the spiro[4.5]-cyclohexadiene system \textbf{3.45} (path \textit{a}), or by \(6\pi\) disrotatory electrocyclic ring opening to the oxepine \textbf{3.46} (path \textit{b}). Path \textit{a} produces the spiro[4.5]-cyclohexadiene motif present in natural products such as the fistularins and aerothyonins. Base-mediated rearomatization of \textbf{3.45} to arene \textbf{3.47} was demonstrated in the context of aerothyonin by Fattorusso and co-workers\textsuperscript{18,19} and leads to natural products with oxidation \textit{ortho} to the three carbon chain such as the purealidins.\textsuperscript{20}

Intermediate \textbf{3.45} can also be hydrolyzed to bromohydrin ketones such as \textbf{3.48}, which make up the agelorins,\textsuperscript{21} dideoxyagelorins,\textsuperscript{22} agelocaissarines,\textsuperscript{23} and aplysinones.\textsuperscript{24} Dehydration of \textbf{3.48} produces spirodienone \textbf{3.49}, a moiety present in purpurealidine B\textsuperscript{25} and clavatadines C and D.\textsuperscript{26} Dehydrobromination of \textbf{3.48} instead would produce epoxide \textbf{3.50} which is present in the calafianins\textsuperscript{27} and aplysinone C.\textsuperscript{22} If instead path \textit{b} predominates, an isomerization of the alkene in
oxepin 3.46 into conjugation with the oxime would provide intermediate 3.51. Oxidation of this intermediate results in a high energy epoxide 3.52 which can be opened by the neighboring oxime, giving the structure 3.53 which possesses the 2° alcohol and the spirooxepin-isoxazoline ring system present in the psammaplysins.

Scheme 3.1 The proposed biosynthesis of bromotyrosine derived natural products

3.3 Previous Synthetic Efforts Towards the Psammaplysins

Although no completed total syntheses have yet been reported, several model studies have been disclosed as strategies towards forming the spirooxepin-isoxazoline ring fusion. Mioskowski’s model study began by generating α,γ-diketoester 3.55 from ketone 3.54. Chemoselective condensation of hydroxylamine onto the more electron-deficient ketone along with loss of water gave spiroisoxazoline 3.56 in 68% yield (Scheme 3.2a). In a 2010 review, Lindel describes this
methodology as “The most promising model study towards [the psammaplysins].” Hamme and co-workers have disclosed a strategy that starts from an isoxazoline 3.58 which is generated by a 1,3-dipolar cycloaddition of alkyne 3.57 and an *in situ* generated nitrile oxide. When treated with a source of electrophilic bromine the spiroisoxazoline 3.59 is formed in good yields, via intramolecular opening of the bromonium by the alcohol (Scheme 3.2). Both strategies successfully generate a spiroisoxazoline ring fusion; however, neither approach demonstrated the ability to access structures with the correct oxidation state present in the psammaplysins at C1.

**Scheme 3.2** Methodology for spiroisoxazoline ring formation via *a.* condensation *b.* bromonium formation

In work unrelated to the psammaplysins, Lieberkinecht and co-workers also demonstrated the utility of a 1,3-dipolar cycloaddition to generate a spiroisoxazoline, except they started with the exocyclic alkene 3.60 and treated with mesitylnitrile oxide to produce the spiroisoxazoline 3.61 directly (Scheme 3.3).
Although they were successful in forming spiroisoxazole ring fusion products, the three model systems lacked much of the functionality present in the psammaplysins, most notably the oxepin portion of the core.

### 3.4 Retrosynthetic Analysis of Psammaplysin

The highly oxidized spirooxepin-isoxazoline ring fusion 3.53 can be thought of as the product of two brominations and a methyl enol ether formation from spirocycle 3.62. This intermediate could further be deconstructed via a series of condensations from an acyclic precursor such as 1,2,4,7,9-pentacarbonyl 3.63 (Scheme 3.4).

**Scheme 3.4** Condensation disconnections to reveal a latent 1,2,4,7,9-pentacarbonyl moiety

Although these disconnections may not be practical in the forward sense, it is important to recognize the latent 1,2,4,7,9-pentacarbonyl moiety as a key structural feature of the psammaplysins.
**Scheme 3.5** Retrosynthetic analysis with key donor-acceptor cyclopropane fragmentation and oxocarbenium trapping

The most logical first retrosynthetic disconnection from 3.53 is an amide coupling to append the side chain, allowing for late-stage analogue synthesis (Scheme 3.5). Heterocycle 3.64 would come from a late stage bromination and methyl vinyl ether formation of 3.65. The spirocycle formation would come from attack of the pendant oxime onto an oxocarbenium generated from the ring fragmentation of a donor-acceptor cyclopropane (DAC) 3.67. The diastereoselectivity of the spiroketal forming step was envisioned to be controlled by the vicinal 2° alcohol stereocenter. The donor acceptor cyclopropane would come from either direct cyclopropanation of a pyrone 3.68, or a dihydropyrone which bears a β-leaving group 3.69.

### 3.4.1 Alpha-Ketol Rearrangement

We recognized from the outset that psammmaplysin had the ability to undergo an alpha-ketol rearrangement\(^\text{32}\) between the oxime imine and 2° alcohol (Scheme 3.6). Since the psammmaplysins have always been isolated as their (−)-(S,S) isomer it is unlikely that an alpha-ketol rearrangement happens readily. To learn more we enlisted the help of graduate student researcher Hung Pham in the Houk lab at UCLA. He performed ground state energy calculations of the simplified core 3.70 and
its alpha-ketol rearrangement product possibilities 3.71–3.74 and found that indeed the natural (S,S) configuration is thermodynamically favored.\textsuperscript{33} Under equilibrating conditions one could envision synthetically accessing the unnatural diastereomer 3.71, the enolamine 3.72, or either of the ketoamines 3.73 or 3.74, then funneling to the desired psammaplysin core 3.70.

\textbf{Scheme 3.6} \(\alpha\)-Ketol rearrangement possibilities with computed ground state energies

\[
\begin{align*}
\text{(S,S)-natural core} & \quad \Delta G \text{ 0.0 kcal/mol} \quad \Delta H \text{ 0.0 kcal/mol} \\
\text{(S,R)-unnatural core} & \quad \Delta G \text{ 3.4 kcal/mol} \quad \Delta H \text{ 3.4 kcal/mol} \\
\text{enolamine 3.72} & \quad \Delta G \text{ 8.6 kcal/mol} \quad \Delta H \text{ 8.4 kcal/mol} \\
\text{ketoamine 3.73} & \quad \Delta G \text{ 5.0 kcal/mol} \quad \Delta H \text{ 5.1 kcal/mol} \\
\text{ketoamine 3.74} & \quad \Delta G \text{ 9.4 kcal/mol} \quad \Delta H \text{ 9.6 kcal/mol}
\end{align*}
\]

3.4.2 Donor-Acceptor Cyclopropane Ring Expansion Strategies

A donor-acceptor cyclopropane (DAC) 3.75 is a unique type of functionality in which the synergistic effect of an electron donor group vicinal to an electron acceptor on a cyclopropane ring causes a very predictable fragmentation pattern 3.76 (Scheme 3.7a).\textsuperscript{34} A typical example of a DAC is one that bears oxygen as the donor group and a ketone group as the acceptor, such as 3.77. Upon fragmentation the zwitterionic charges are stabilized by the donor-acceptor system in the form of an oxocarbenium ion and enolate 3.78. The zwitterion can be quenched to produce 1,4-diketones 3.79,
or react with nucleophiles and electrophiles to generate compounds such as \textbf{3.80}, or even react to yield formal [3+2] cycloaddition products \textbf{3.81} (Scheme 3.7b).\textsuperscript{35,36} The umpolung reactivity of DACs provides products not easily accessible by alternative chemistry.

\textbf{Scheme 3.7 a.} Donor-acceptor cyclopropane fragmentation pattern \textit{b.} Umpolung reactivity of donor-acceptor cyclopropanes

The most common preparations of donor-acceptor cyclopropanes involve the reaction of a carbene equivalent with an alkene. The disconnection possibilities include: a) a donor-acceptor alkene reacting with a methylene carbene; b) an electron rich alkene reacting with an electron-deficient carbene; c) an electron-rich carbene reacting with an electron-deficient alkene (Scheme 3.8). For each of these synthons there is a corresponding methodology for the preparation of donor-acceptor cyclopropanes in a formal [2+1] reaction.

\textbf{Scheme 3.8} Carbene disconnection strategies for cyclopropane synthesis
The Simmons–Smith reaction is a well-known method for generating a carbene equivalent that reacts with alkenes to produce cyclopropanes.\textsuperscript{37–39} Zercher has extended this methodology to homologate \(\beta\)-keto esters \textbf{3.82} through the intermediacy of a DAC \textbf{3.83} to produce \(\gamma\)-keto esters \textbf{3.84} (Scheme 3.9a).\textsuperscript{40–42} Metal catalyzed reactions of \(\alpha\)-diazocarbonyls \textbf{3.86} with enoxy groups \textbf{3.85} are another well-established method for generating DACs. This method has been rendered enantioselective with the use of chiral catalysts and chiral auxiliaries (Scheme 3.9b). Fischer carbene complexes \textbf{3.88} are known to react with electron-deficient olefins, usually at elevated temperatures, leading to the formation of DACs \textbf{3.90} (Scheme 3.9c).\textsuperscript{35}

**Scheme 3.9 a.** Zercher’s \(\beta\)-keto ester homologation strategy b. Enantioselective generation of DACs via reaction of \(\alpha\)-diazocarbonyl with electron rich alkenes c. Fischer carbene reacting with electron-deficient alkenes to produce DACs

In a context more related to the synthesis of psammaplysins, a few synthetic strategies have utilized a donor-acceptor cyclopropane for the ring expansion of dihydropyrones. Sridhar has developed a protocol to provide septanohexose mimics for pyranose and furanose sugars.\textsuperscript{43} The protocol required a Luche reduction of the dihydropyrene \textbf{3.91} to the allylic alcohol, followed by Simmons–Smith
cyclopropanation, directed by the alcohol. The cyclopropylcarbinol was then reoxidized to the donor-acceptor cyclopropane 3.92 in 80% yield over 3 steps (Scheme 3.10). The DAC 3.92 could then be subjected to Lewis acidic conditions and trapped intermolecularly with the 1° alcohol of another sugar.

**Scheme 3.10** DAC ring expansion strategy of a dihydropyran via fragmentation and oxygen trapping

DACs can also be fragmented and trapped with carbon nucleophiles as well. Sugita has shown that donor-acceptor cyclopropane 3.96, prepared in the same three step manner from the dihydropyran 3.95, could be fragmented in the presence of a Lewis acid and an enoxysilane to give the ring expanded product 3.98 in good yields (Scheme 3.11).44,45

**Scheme 3.11** DAC ring expansion strategy of a dihydropyran via fragmentation and carbon nucleophile trapping

In both reports, no mention was made about attempting to directly cyclopropanate the dihydropyran. Presumably, if cyclopropanation were to occur, the DAC would fragment prematurely under the Lewis acidic conditions of the reaction. Also, Simmons–Smith
cyclopropanations work best on olefins with an alcohol at the allylic position. The alcohol activates and directs Simmons–Smith cyclopropanation.\(^{46-50}\)

### 3.4.3 Strategies for α-Oximinoamide Synthesis

The prevalence of α-oximinoamide containing natural products has resulted in a number of elegant strategies for generating α-oximinoacids—which can easily be transformed into the corresponding amide. The simplicity of generating α-oximinoacids via condensation of hydroxylamine onto an α-ketoacid has been recognized by several groups in the context of the synthesis of psammaplin A. Hoshino and Nicolaou both accessed α-ketoacid 3.99; Nicolaou opted to perform a condensation to provide the THP-protected α-oximinoacid 3.100, while Hoshino condenses on hydroxylamine to provide the free α-oximinoacid 3.101 (Scheme 3.12).\(^{51-53}\)

**Scheme 3.12 Syntheses of psammaplin A utilizing condensation for generating an α-oximino acid**

In his synthesis of psammaplin A 3.102, Fuchter originally attempted to make use of an Erlenmeyer oxazalone method for the synthesis of α-ketoacid 3.105 from benzaldehyde 3.103, however yields suffered when there was bromine substitution of the arene (Scheme 3.13a). Fortunately, he was able
to utilize a Knoevenagel–Doebner approach for the bromine substituted aldehyde 3.106 to generate α,β-unsaturated ester 3.107. Dihydroxylation of 3.107 followed by treatment of acid generated an α-ketoester, which after condensation with hydroxylamine provided the α-oximinoamide 3.108 (Scheme 3.13b).

Scheme 3.13 Fuchter’s preparations of a. an α-keto acid via an Erlenmeyer oxazalone strategy b. an α-keto ester via a Knoevenagel–Doebner strategy

Perhaps an even more direct preparation of α-oximinoesters had already been developed by Spilling and co-workers. For the synthesis of purealidin N 3.112, they performed a Horner–Wadsworth–Emmons olefination onto a highly substituted benzaldehyde 3.109 to generate enoxysilane 3.110. Careful single-pot deprotection and oxime formation afforded α-oximinoester 3.111 in excellent yield (Scheme 3.14).
Scheme 3.14 Horner–Wadsworth–Emmons strategy for preparation of α-oximinoamides

Another clever demonstration of accessing α-oximinoamides was by Wasserman in his synthesis of verongamine 3.115. A phosphocyanoylide was coupled with carboxylic acid 3.113 to generate the α-cyanoylide 3.114. Ozonolysis of the phosphorous ylide generates an acylcyanide which is used to couple on a histamine side chain. Reacting with hydroxylamine gives verongamine 3.115 in short order and acceptable yields (Scheme 3.15). 56

Scheme 3.15 Cyanoylde coupling strategy for the preparation of α-oximinoamides

There are select examples of generating α-oximinoesters other than condensation, such as that reported by Spilling where he converts α-aminoester 3.116 directly to the α-oximinoester 3.117 via oxidation of the amine, with DMDO being the most practical oxidant (Scheme 3.16). 55
**Scheme 3.16** Direct oxidation of $\alpha$-aminoesters to $\alpha$-oximinoesters

![Scheme 3.16](image)

### 3.5 Conclusions

Despite their promising biological activity, there are no published syntheses of any member of the psammaplysin family to date. Due to the dearth of naturally occurring material, a concise synthesis will be necessary to establish a more comprehensive biological evaluation of the psammaplysins and to discover more active analogs.

At the outset of this project there were many unanswered questions about the best way to access the intermediate **3.67** necessary to try the DAC fragmentation strategy. It was not clear that previously worked out methodology for DAC formation and $\alpha$-oximinoester formation was going to be possible in the context of psammaplysin. Given that there were many conceivable ways of accessing **3.67**, and in the spirit of discovery, we decided to proceed forward at first with some very different strategies from what others had done.

### 3.6 References


(33) Pham, H. K. B3LYP/6-31G(d), gas phase.


Chapter 4: Studies Towards the Psammaplysin Family of Natural Products

At the outset of this project there were many questions about the how to build up functionality and execute the key spirocycle forming step. What initiated were several model studies that were designed to answer key questions: 1) how best to introduce the donor-acceptor cyclopropane (DAC); 2) how best to introduce the secondary alcohol; and 3) how best to introduce the oximinoamide portion of the molecule (Figure 4.1). What was discovered led to a strategy that introduces the DAC that could be fragmented and trapped by an oximino ester to generate the spirocyclic skeleton of psammaplysin.

Figure 4.1 Functionality required for assessing the key step

4.1 Proof of Concept

It was unknown at the outset if pyrones or dihydropyrones could be cyclopropanated in one step. An anticipated outcome was that the cyclopropanation conditions would generate the DAC adduct 4.2 and in the same pot fragment to reveal the oxocarbenium 4.3. One-step cyclopropanation-fragmentation might be an undesired pathway for a procedure that sought to engage the oxocarbenium 4.3 with an exogenous nucleophile; however, the ability to cyclopropanate and in the same pot fragment and trap intramolecularly to form the spirooxepin-isoxazoline 4.4 would greatly increase complexity in a single step (Scheme 4.1).
To test the viability of this approach, a model system was designed that did not contain the oximinoamide moiety. Pyrone 4.5 and dihydropyrone 4.6 were prepared using a procedure adopted from Koreeda.\(^1\) Unfortunately, multiple attempts at the cyclopropanation of either using Simmons–Smith,\(^2\)–\(^7\) Corey–Chaykovsky conditions, or modifications thereof resulted in no reaction or decomposition. It could be expected that the aromatic character of 4.5 likely contributes to the observed poor reactivity; however, the non-aromatic substrate 4.6 also demonstrated no reactivity towards a variety of cyclopropanation conditions (Scheme 4.2). When 4.6 was reduced with DIBALH, a diastereotopic mixture of allylic alcohols 4.9 resulted. The allylic alcohol 4.9 was cyclopropanated under Simmons–Smith conditions in 95% yield to afford 4.10. Reoxidation of the alcohol to the ketone worked best under Swern conditions to give the DAC in 84% yield. Treatment with \(p\)-TsOH in the presence of methanol gave 4.11 as an inseparable mixture of diastereomers.
This result proved that the one-step cyclopropanation/fragmentation was not viable, but a three step sequence of reduction/cyclopropanation/oxidation of dihydropyrone was viable. However, questions still remained, such as the ability of the β-methoxide leaving group to be easily eliminated to provide the unsaturation present in the psammmaplysins, and how to incorporate the α-oximino acid portion of the molecule.

4.2 Nitroaldol Disconnection Strategy

The nitroaldol reaction (also known as the Henry reaction) has shown vast utility for generating β-hydroxynitro compounds from the corresponding aliphatic nitro and aldehyde starting materials. Under the appropriate reaction conditions the relative stereochemistry between the vicinal nitro and hydroxy can be controlled. In the context of this synthesis, the stereochemistry of the nitrogroup is inconsequential since it will be converted to an oxime. However, in order to develop an asymmetric synthesis, absolute stereocontrol of the secondary alcohol is essential; fortunately numerous examples of asymmetric nitroaldol reactions exist.
The synthesis would commence with an asymmetric nitroaldol coupling between aldehyde 4.12 and ethyl nitroacetate 4.13. Deoxygenation using Carreira’s method,\textsuperscript{19} followed by the three step cyclopropanation sequence (reduction, Simmons–Smith, oxidation) would provide key intermediate 4.15 (Scheme 4.3).

**Scheme 4.3** Nitroaldol approach to the psammaplysin core

![Scheme 4.3](image)

To quickly evaluate the key chemistry, we chose to start with dihydropyrones 4.16 and 4.17, which can be accessed in one step from commercially available starting materials via known chemistry.\textsuperscript{20} Although these substrates lacked the pyrone oxidation state necessary for the psammaplysins, it was envisioned that if this strategy worked well, the lacking oxidation could be addressed at a later time. These substrates were useful because they not only provided an allylic mono- (4.16) or di- bromide (4.17) as a handle to introduce the aldehyde, but they also possessed the vinyl bromide present in the natural product (Scheme 4.4).
Multiple attempts at converting either 4.16 or 4.17 into the vinylogous ketoaldehyde 4.18 were met with failure. Although allylic bromide 4.16 was easily converted to the allylic alcohol with silver trifluoroacetate, all attempts to oxidize it to the aldehyde 4.18 caused decomposition. Direct conversion of 4.16 to the aldehyde using Kornblum oxidation conditions\textsuperscript{21} also caused decomposition. Subjecting germinal dibromide 4.17 to silver trifluoroacetate in another attempt to access aldehyde 4.18 in one step also caused decomposition. It became apparent that the aldehyde could be made and observed in the crude reaction mixture by NMR; however, it was not amenable to isolation without decomposition. In light of this, the cyclic vinylogous ester 4.17 was reduced and protected as the allylic alcohol 4.19—the reduction being necessary eventually as part of the three step cyclopropanation sequence. The reduced and protected product could now be easily converted into the aldehyde 4.20 by treatment with silver trifluoroacetate or potassium superoxide.

With aldehyde 4.20 in hand, the nitroaldol reaction was attempted with doubly-deprotonated nitroethane as the nucleophile. The dianion nucleophile was chosen because it tends to limit the amount of β-hydroxide elimination compared to the conventional Henry reaction, provided that a careful workup is performed. Isolation of the desired product 4.21 as a mixture of four separable
diastereomers in greater than 70% yield. Unfortunately, several attempts at dehydrating 4.21 using Carreira’s method were unsuccessful (Scheme 4.5). The ability of the β-alcohol to be benzylated or eliminated under Carreira’s conditions caused us to once again rethink our strategy.

Scheme 4.5 Attempts at deoxygenating a secondary nitro group to an oxime

It was thought that if the allylic alcohol 4.23 could be cyclopropanated and oxidized to DAC 4.24, under the fragmentation conditions the oxocarbenium that formed could be trapped by the nitro to give the spiroisoxazoline-N-oxide 4.25. Deoxygenation of the spiroisoxazoline-N-oxide at this stage might not be complicated by β-elimination side product formation (Scheme 4.6a).

Scheme 4.6a. Strategy for spiroisoxazoline-N-oxide formation and late stage deoxygenation b. Jørgensen’s isoxazoline-N-oxide formation and deoxygenation sequence

In a similar fashion, Jørgensen and co-workers have prepared isoxazoline-N-oxides such as 4.29 via an α-bromination/nitroaldol cyclization sequence using enantioselective organocatalysis. They were
then able to deoxygenate in a two-step procedure to provide the isoxazoline 4.30 in 96% yield (Scheme 4.6b).\textsuperscript{22}

Given this promising precedent, we shifted focus to cyclopropanating the allylic alcohol 4.23, afforded after a deprotection of nitroaldol product 4.21. Unfortunately, the cyclopropanation conditions that worked on the proof of concept only returned starting material or decomposition. The presence of the vinyl bromide in this series is likely the problem, with the tetrasubstituted olefin being a much more challenging cyclopropanation substrate compared to the trisubstituted 4.9 (Scheme 4.7).\textsuperscript{7}

**Scheme 4.7** Cyclopropanation attempts to access a spiroisoxazoline-\(N\)-oxide

![Scheme 4.7](image)

The challenges encountered with this route prompted a shift towards the exploration of other routes for assessing the key DAC fragmentation step. However, questions still remained on the viability of this methodology. The most advanced intermediate 4.23 lacked the oxidation state of the oximinoamide portion of psammaplysin; however, performing the nitroaldol reaction with ethyl nitroacetate would easily solve this problem by bringing in the desired ester oxidation state.

**4.3 Oxime Anion Additions to 4-Ethoxy-5,6-dihydro-2H-pyran-2-one**

We next considered a strategy that would directly incorporate the oxime and secondary alcohol moieties in a convergent manner. It is known that lithiated oximes and \(O\)-silyloximes are competent carbon nucleophiles.\textsuperscript{23–27} Inspiration was drawn from chemistry developed by Winkler in choosing
an appropriate electrophile to react with an oxime anion. Winkler was able to prepare a variety of 6-alkyl-5,6-dihydro-2\(H\)-pyran-2-ones such as 4.33 via a hetero-Diels–Alder between Brassard’s diene 4.32 and an aldehyde. A variety of organometallic nucleophiles could be added into the C2 carbonyl; however, the example the enolate of ethyl isobutyrate 4.34 stood out as very similar to a lithiated oxime (Scheme 4.8).

**Scheme 4.8** Winkler’s methodology for generating 2\(H\)-dihydropyrone and nucleophilic addition to generate 4\(H\)-dihydropyrone

By adopting Winkler’s strategy, pyrone 4.36 could be prepared in 43% yield from the hetero-Diels–Alder of Brassards diene 4.32 and formaldehyde. The low yield was due to mono-addition side products; all attempts to increase the yield by modifying the temperature, Lewis acid, or varying the source of formaldehyde failed to increase the yield. We considered that pyrone 4.36 would be an ideal electrophile for the addition of a lithiated oxime to produce a 4\(H\)-pyrone 4.37 that possessed the requisite oxime and secondary alcohol functionality present in the psammaplysins. From there, the three step cyclopropanation sequence would yield the donor-acceptor cyclopropane 4.38, which upon fragmentation would provide spirocycle 4.39. If successful, only a few more steps would be required to access the psammaplysins (Scheme 4.9).
With pyrone 4.36 in hand, several oxime anion nucleophiles were surveyed. The best case scenarios involved adding doubly lithiated oximes such as 4.41 and 4.42 that possessed some of the oxidation present in psammamaplysin. When these failed to undergo the addition into the pyrone several variants were tried, such as the O-silyloximes 4.43 and 4.44, and the ketone variants 4.45 and 4.46. Unfortunately we were never able to observe any products resulting from addition of these substrates into the pyrone, despite control experiments that confirmed their ability to add into simpler substrates (Scheme 4.10).

The only nucleophiles that gave any indication of adding into 4.36 were acetone oxime 4.47 and the oxidized variant 4.48 to provide the cyclic α,β,γ,δ-unsaturated compounds 4.49 and 4.50. Treatment
with $p$-TsOH hydrolyzed the ethyl enol ether, providing the cyclized products 4.51 and 4.52 in poor yields (Scheme 4.11).

**Scheme 4.11** Oxime anion nucleophilic addition into 2$H$-pyrone using 

\[ a. \text{ acetone oxime} \quad b. \text{ $\alpha$-siloxy acetone oxime} \]

The alkene in 4.51 and 4.52 was not in conjugation with the pyrone as initially expected; rather the unsaturation was in conjugation with the oxime. This interesting feature precluded the possibility of making the desired donor-acceptor cyclopropane for ring expansion. However, there was still an opportunity to perform a ring expansion by making a different donor-acceptor cyclopropane. Motivation came from a study by Zercher where he demonstrated homologation of $\beta$-keto esters such as 4.54 into $\gamma$-keto esters (4.56) through the intermediacy of a donor-acceptor cyclopropane (4.55). \(^{30,31}\) Gratifyingly, when vinylogous dicarbonyl 4.51 was subjected to the Simmons–Smith conditions, the ring expanded product 4.58 was isolated (Scheme 4.12). Attempts at derivatizing and crystallizing 4.58 for X-Ray crystallographic analysis were unsuccessful and difficult given the lack of material and the tendency for 4.58 to decompose.
Although a promising result, the chemistry developed to access the seven membered ring 4.58 was very poor yielding and did not allow for the incorporation of much of the desired oxidation present in psammaplysins. We decided that this approach in its current form would not make for a very attractive synthesis given the multiple low yielding steps. Concurrently, another strategy was being explored that was proving to be more fruitful, one that could potentially incorporate the correct oxidation pattern present in the psammaplysins quickly and efficiently.

### 4.4 Ketene Diels–Alder Disconnection Strategy

The culmination of efforts towards the psammaplysins up to this point reinforced the notion to develop a synthesis that rapidly builds complexity from simple starting materials and possess an oxidation pattern very similar to the psammaplysins. The ketene Diels–Alder strategy discussed herein drew inspiration from a report by Crimmins that described the preparation of 4H-pyrones from dioxinones for the synthesis of the AB spiroketal moiety of spongistatin. Crimmins started from silyl ketene acetal 4.59, prepared easily from the corresponding dioxinone, and did an addition into aldehyde 4.60. A BOM protection was necessary for the next step, in which a thermal retro
[4+2] produced the acyl ketene 4.62, which in the presence of excess n-butyl vinyl ether underwent a [4+2] to produce dihydropyrole 4.63. Treatment of 4.63 with p-TsOH caused elimination of the β-butenol, revealing pyrone 4.64, which was taken on five steps to the AB spiroketal ring fusion present in spongistatin 4.65 (Scheme 4.13).

Scheme 4.13  Crimmins synthesis of the AB spiroketal moiety of spongistatin using a ketene Diels–Alder strategy

The significance of this precedent was the ability to rapidly bring two fragments together and generate a dihydropyrole 4.63 that possessed the latent functionality of a pyrone 4.64 in the form of a hemiacetal at C2. The initial plan to apply this strategy towards the synthesis of the psammamplings was to add the same silyl ketene acetal 4.59 into ethyl glyoxylate and oxidize to the carbonyl 4.66. Thermolysis of the dioxinone followed by a ketene [4+2] would provide dihydropyrole 4.67, which after a series of manipulations including the three step cyclopropanation sequence would provide the carbon skeleton 4.68 in short order (Scheme 4.14).
The addition of silyl ketene acetal 4.59 into ethyl glyoxylate proceeded smoothly, as did protection as the BOM ether (not shown) or silyl ether 4.69. The BOM protected intermediate was successfully advanced several steps into the synthesis; however, late stage deprotection was problematic. The TBS protected substrate 4.69 successfully underwent thermolysis and ketene [4+2], which was subsequently deprotected to provide the alcohol 4.70. At this stage there was considerable difficulty oxidizing the alcohol to the α-ketoester 4.67 without significant decomposition (Scheme 4.15a).

**Scheme 4.14** Dioxinone thermolysis and ketene [4+2] strategy for synthesis of the carbon skeleton

**Scheme 4.15** Dihydropyrene formation by addition of silyl ketene acetal 4.59 into *a.* ethyl glyoxylate *b.* ethyl chlorooxooacetate
Taking a step back, it became apparent that the most efficient entry into this class of compounds would be to directly access the α-ketoester oxidation state, rather than attempt an oxidation state manipulation. To this effect, an acylation of silyl ketene acetal 4.59 with ethyl oxalyl chloride was performed to provide the desired α-ketoester 4.71 in 37% unoptimized yield. The silylated α-oximinoester 4.72 could be generated in a single step via condensation of O-(tert-butyldimethylsilyl)hydroxylamine onto the ketone. The same compound can be generated in higher yields via a two-step procedure by condensing hydroxylamine onto the ketone to provide 4.73, followed by treatment with TBSCI. The thermolysis of dioxinone 4.72 and ketene [4+2] provided the desired dihydropyrene 4.74 in 57% yield (Scheme 4.15b).

**Scheme 4.16** Three step reduction/cyclopropanation/oxidation sequence to afford the requisite donor-acceptor cyclopropane

The three step cyclopropanation sequence effectively provided the donor-acceptor cyclopropane 4.75 without the need for much optimization (Scheme 4.16). This was the first instance where we were able to access a donor-acceptor cyclopropane that possessed the desired 1,2,4,7,9-pentacarbonyl oxidation pattern and thoroughly evaluate the proposed DAC fragmentation/trapping step.
At first, ambitious attempts were made to find conditions that would fragment the DAC 4.75, cleave the O-silyloxime and eliminate n-butanol to access either 4.68 or 4.80 in a single pot. Although not successful, several intermediates were isolated that resulted from the trapping of the oxocarbenium via elimination (4.76), with H₂O (4.77), or with a protic solvent (4.78, 4.79). Attempts to convert these intermediates to the desired products 4.68 or 4.80 via desilylation, Brønsted acidic, or Lewis acidic conditions never produced anything more than products arising from hydrolysis or decomposition (Scheme 4.17).

With this result, we focused our efforts on a strategy that more closely resembled the original retrosynthesis, which called for a free oxime to be present at the DAC fragmentation event. In that vein, the O-silyloxime 4.81 was deprotected and subsequently subjected to PCC oxidation conditions. The DAC that is formed fragmented under the reaction conditions to provide spiroisoxazoline 4.82 as a mixture of diastereomers. The two step process was not very high yielding; however, neither reaction was extensively optimized. Treatment of the spiroisoxazoline
4.82 with p-TsOH prompted the elimination of butanol, which was desired; however, it also caused opening of the isoxazoline to provide 4.80 (Scheme 4.18).

**Scheme 4.18** Donor-acceptor cyclopropane fragmentation in the presence of a free oxime

The dihydrooxepin 4.80 was prone to decomposition, which contributed to the low yield. However, there was great opportunity in this result: the α,β-unsaturation of the oxime 4.80 could be a handle for a “biomimetic” oxidative installation of the secondary alcohol and reformation of the spirocycle (Scheme 4.19). Alternatively, with careful optimization of the elimination conditions it might be possible to isolate the intermediate spirooxepin-isoxazoline 4.68, which could open new avenues for elaborating to the psammaplysins.

**Scheme 4.19** Future directions for elaboration to the psammaplysins

4.5 **Incorporation of the Secondary Alcohol and Future Directions**

Once this strategy had been developed for formation of the spirooxepin-isoxazoline carbon skeleton 4.82, our attention shifted to how best to incorporate the secondary stereogenic alcohol. Installation
of the secondary alcohol late stage might be a viable option; however, a more attractive strategy would be to incorporate the secondary alcohol earlier in the synthesis.

4.5.1 Early Stage Oxidation for Incorporation of Secondary Alcohol

Certainly there is a great body of work in performing allylic oxidations\(^\text{35}\) or oxidations alpha to a carbonyl such as the Rubottom oxidation.\(^\text{36,37}\) The Abe group was able to demonstrate the oxidation of dioxinone \(4.84\) by formation of the silyl dienol ether \(4.59\) followed by treatment with triphenyl phosphite ozonide to provide a mixture of the alcohol \(4.85\) and peroxide \(4.85\) (Scheme 4.20a).\(^\text{38}\) This precedent prompted us to initially attempt a Rubottom oxidation. The dioxinone intermediate \(4.72\) was an attractive starting point for incorporation of the secondary alcohol for three reasons: 1) the dioxinone was an early stage intermediate; 2) either Rubottom or allylic oxidation conditions could be attempted; 3) the other functionality on the molecule would not react under the Rubottom oxidation conditions. Formation of the silyl ketene acetal \(4.87\) was successful as observed by crude NMR, and chemoselective oxidation provided the desired product \(4.88\) in 21\% yield over two steps (Scheme 4.20b). These results were preliminary and the yield might be improved in the future.

**Scheme 4.20** Allylic oxidation of a dioxinone \(a\). by the Abe group using triphenyl phosphite ozonide \(b\). using Rubottom conditions to introduce the secondary alcohol present in the psammaplysins
It was very promising that we were able to access intermediate 4.88 that possessed the secondary alcohol. If this substrate proves amenable to the subsequent steps that have already been demonstrated to access less oxidized 4.82, then it might be possible to access spiroisoxazoline 4.91, which contains almost all of the desired functionality present in the psammaplysins. Presumably, with the secondary alcohol present, elimination of butanol can be achieved without concomitant spiroisoxazoline ring opening. From there, exploration can begin on the final three steps in the synthesis: bromination, methylation, and amide coupling (Scheme 4.21).

Scheme 4.21 Future directions for elaboration using a ketene Diels–Alder strategy

4.5.2 Conversion of Aliphatic Nitro Compounds into α-Siloxyoximes

The acyl ketene Diels–Alder strategy proved to be very effective at producing dihydropyrones that could easily be converted into the corresponding pyrone, introducing much of the correct oxidation present in the psammaplysins. Given its utility, there are possibly more opportunities for a synthesis of the psammaplysins using the ketene-Diels–Alder strategy. Ioffe and co-workers have demonstrated the ability to convert aliphatic nitro compounds 4.93 into α-hydroxyoximes 4.95 in a two-step procedure that proceeds through the intermediacy of an \( N,N \)-bis(siloxy)enamine 4.94 (Scheme 4.22a). \(^{39–42}\) Utilizing the ketene Diels–Alder strategy, allylic bromide 4.96 was prepared in
two steps from commercial dioxinone \(^{4,84}\). DIBALH reduction furnished an allylic alcohol, which was prone to decomposition, but could be immediately silylated to provide the stable dihydropyronone \(^{4,97}\). Since \(\alpha\)-alkylations of nitro compounds are well preceded,\(^{45-47}\) it may be possible to develop a coupling of ethyl nitroacetate and allylic bromide \(^{4,97}\) to produce the aliphatic nitro compound \(^{4,98}\). Adopting Ioffe’s method could, in a single pot, provide compound \(^{4,99}\) bearing the \(\alpha\)-oximino ester and secondary alcohol (Scheme 4.22b).

**Scheme 4.22 a.** Ioffe’s methodology for conversion of aliphatic nitro compounds into \(\alpha\)-siloxoyximes b. Ketene Diels–Alder strategy to possibly generate aliphatic nitro compound

4.6 Conclusions

A strategy was realized that closely resembled the original retrosynthetic analysis and was able to provide compounds resembling the spirocyclic skeleton of psammaplys in with nearly all of the correct oxidation states. In the future, this route could conceivably be developed into an efficient total synthesis of all of the psammaplysins and analogue thereof.
4.7 Experimental Procedures

General Experimental Protocols

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Reaction solvents including dichloromethane, toluene, benzene, N,N-dimethylformamide, and tetrahydrofuran were dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon. Column chromatography was performed using 60 Å (0.040–0.063 mm) mesh silica gel (SiO₂). The following reagents were distilled from the indicated drying agents under argon prior to use: triethylamine (CaH₂), N,N-diisopropylethylamine (CaH₂), trimethylsilyl chloride (TMSCl, CaH₂), n-butylvinylether (Na⁰), 2,2,6-trimethyl-4H-1,3-dioxin-4-one, and ethyl chlorooxacetate, nitroethane. CH₂I₂ was dried using MgSO₄, distilled from fine Cu⁰ shavings under argon. Acetone oxime was sublimed prior to use. Dess–Martin periodinane, n-butyllithium, imidazole, camphorsulfonic acid (CSA), sodium borohydride, N-chlorosuccinimide, N-bromo succinimide, t-butyldimethylsilyl chloride, diisobutylaluminum hydride (DIBALH), pyridinium chlorochromate (PCC), para-toluenesulfonic acid monohydrate (p-TsOH·H₂O), lithium borohydride (LiBH₄), (E)-4-methoxybut-3-en-2-one, silver trifluoroacetate (AgTFA) and paraformaldehyde were used without further purification. Monomeric “cracked” formaldehyde, § 2,2-dimethyl-1,3-dioxan-5-one, 28 $O$-(tert-butyl dimethylsilyl)hydroxylamine 49 were prepared according to literature procedures. ¹H and ¹³C spectra were referenced to residual solvent (CDCl₃: 7.26 ppm, ¹H, 77.16 ppm, ¹³C; C₆D₆: 7.16 ppm, H¹, 128.06 ppm, C¹³). Chemical shifts are reported in parts per million, and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), m (multiplet), br (broad), and app (apparent). Coupling
constants, $J$, are reported in Hertz. Infrared (IR) spectra were recorded on an FT-IR instrument on NaCl plates, and peaks are reported in cm$^{-1}$. High-resolution mass spectra (HRMS) data are reported in the form of $(m/z)$. Kugelrohr distillation temperatures reported are air bath temperatures (ABT). Visualization of analytical thin-layer chromatography was accomplished with UV(254) and potassium permanganate (KMnO$_4$) or $p$-anisaldehyde staining solutions.

**Proof of Concept**

![Chemical Structure](attachment:image.png)

**bis-tert-Butyldimethylsilyl glycolic acid S1:** A 1 L round bottom flask was charged with glycolic acid (24.1 g, 317 mmol) and DCM (200 mL). The flask was cooled to 0 °C and pyridine (56.4 mL, 2.2 equiv) was added via syringe. A solution of TBSCI (100 g, 2.1 equiv) in DCM (100 mL) was transferred into the flask via cannula using argon pressure. A white precipitate formed before the cannula transfer was complete. The suspension was stirred for 12 hours at 20 °C, then poured over sat. aq. NaHCO$_3$ (50 mL). The biphasic mixture was separated and the aqueous phase was extracted with DCM (3 × 50 mL). The combined organic extracts were washed with H$_2$O (1 × 100 mL), brine (1 × 100 mL) and dried over MgSO$_4$. Filtering and concentrating *in vacuo* provided 120 grams of crude product, which was purified via column chromatography (500 mL SiO$_2$, 10% EtOAc/Hexanes) to provide S1 (89 g, 92% yield) as a white powder. $^1$H NMR (499 MHz, CDCl$_3$) $\delta$ 4.19 (s, 2H), 0.93 (s, 9H), 0.92 (s, 9H), 0.28 (s, 6H), 0.10 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.1, 62.5, 25.9 (3C), 25.7 (3C), 18.6, 17.8, −4.6 (2C), −5.3 (2C).
2-((tert-Butyldimethylsilyl)oxy)acetyl chloride S2: This procedure was adapted from a procedure developed by Wissner. A 100 mL round bottom was charged with TBS ether S1 (7.28 g, 23.9 mmol), DMF (184 μL, 0.1 equiv) and DCM (24 mL). Oxaly chloride (2.26 mL, 1.1 equiv) was added slowly over 10 minutes to the stirring solution via syringe transfer. Gas evolution was observed. After 20 minutes of stirring the mixture was concentrated in vacuo on a rotary evaporator. The crude was subjected to Kugelrohr distillation (10 mmHg, 60 – 70 °C ABT) to remove TBS chloride. The remaining compound was diluted with dry Et2O (5 mL) and used as is in the subsequent reaction.

Dihydropyranone 4.6: A 250 mL round bottom flask was charged with THF (100 mL) and diisopropylamine (2.79 mL, 1.0 equiv) and cooled to −78 °C. n-BuLi [2.57] in hexanes (7.75 mL, 1.0 equiv) was added dropwise via syringe and stirred for 5 minutes. (E)-4-methoxybut-3-en-2-one was added neat, dropwise via syringe. The solution turned deep red immediately and was stirred for 0.5 hour. Acid chloride S2 was added as a solution in Et2O (5 mL) dropwise via syringe followed by 1 hour of stirring. The solution was warmed to −30 °C and allowed to stand for 12 hours. Sat. aq. NaHCO3 (100 mL) was added and the biphasic mixture was separated and the aqueous phase was extracted with Et2O (3 × 100 mL). The combined organic extracts were dried over MgSO4, filtered, and concentrated in vacuo to provide 5.43 g of a crude oil which was purified via column chromatography (100 mL SiO2, 10% EtOAc/Hexanes, Rf = 0.05) to provide 4.6 (710 mg, 13% yield) as an orange oil. 1H NMR (600 MHz, CDCl3) δ 5.60 (s, 1H), 5.24 (m, 1H), 4.13 (s, 2H), 3.43 (s, 3H), 2.67 (dd, J = 16.8, 3.8, 1H), 2.53 (dd, J = 3.8, 16.8, 1H), 0.84 (s, 9H), 0.02 (s, 6H); 13C NMR (126
MHz, CDCl$_3$ δ 190.8, 172.3, 103.0, 102.9, 61.8, 56.8, 42.2, 25.8 (3C), 18.3, –5.5 (2C); IR (thin film) 2955, 2931, 2857, 1680, 1632, 1121, 839 cm$^{-1}$; LRMS (ESI) $m/z$ calcd for C$_{13}$H$_{24}$O$_4$SiNa [M + Na]$^+$ 295.1342, found 295.1222.

(±)-(R,R)-Dihydropyranol 4.9 and (±)-(R,S)-Dihydropyranol S3: A 10 mL sealed tube was charged with PhMe (1.8 mL) and dihydropyrene 4.6 (329 mg, 1.21 mmol) then cooled to –78 °C. DIBALH (105 μL, 1.1 equiv) was added neat via syringe. The solution was stirred for 2 hours, then diluted with Et$_2$O (5 mL) and sat. aq. Rochelle’s salt (5 mL). The biphasic mixture was extracted with Et$_2$O (3 × 4 mL). The combined organic extracts was washed with brine (2 × 2 mL), dried over MgSO$_4$, filtered and concentrated in vacuo to provide the crude product which was purified via column chromatography (60 mL SiO$_2$, 10% EtOAc/Hexanes, $R_f$ = 0.1) to yield the (R,R)-syn product 4.9 (164 mg, 50% yield) and the (R,S)-anti product S3 (74 mg, 22% yield) as clear oils. Data for (R,R) 4.9: $^1$H NMR (500 MHz, CDCl$_3$) δ 5.25 (d, $J$ = 4.6, 1H), 5.16 (s, 1H), 4.04 (app d, $J$ = 6.2, 2H), 4.00 (m, 1H), 3.40 (s, 3H), 2.89 (d, $J$ = 10.7, 1H), 2.23 (d, $J$ = 14.8, 1H), 1.97 (app d, $J$ = 16.1, 1H), 0.91 (s, 9H), 0.09 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 150.5, 101.0, 98.5, 62.8, 59.4, 56.1, 34.8, 26.0 (3C), 18.5, -5.19, -5.21; IR (thin film) 3332 (br), 2953, 2886, 2858, 1470, 1254, 834 cm$^{-1}$; HRMS (ESI) $m/z$ calcd for C$_{13}$H$_{26}$O$_4$SiNa [M + Na]$^+$ 297.1498, found 297.1504. Data for (R,S) S3: $^1$H NMR (500 MHz, CDCl$_3$) δ 5.03 (d, $J$ = 2.9 Hz, 1H), 4.89 (dd, $J$ = 3.6, 5.9 Hz, 1H), 4.33 (d, $J$ = 3.6 Hz, 1H), 4.03 (s, 2H), 3.49 (s, 3H), 2.01 (br s, 1H), 1.91 (t, $J$ = 4.6 Hz, 2H), 0.90 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 153.3, 99.03, 99.00, 62.3, 56.1, 56.0, 56.0, 25.9 (3C), 18.4, –5.26, –5.28; HRMS (ESI) $m/z$ calcd for C$_{13}$H$_{26}$O$_4$SiNa [M + Na]$^+$ 297.1498, found 297.1508.
(±)-(R,S)-Cyclopropylcarbinol S4: A sealed 10 mL vial was charged with (±)-(R,S)-dihydropyranol S3 (87.0 mg, 0.317 mmol), DCM (1.0 mL) and CH₂I₂ (38 μL, 1.5 equiv). The mixture was cooled to −20 °C before neat Et₂Zn (49 μL, 1.5 equiv) was added dropwise via syringe. NOTE: Et₂Zn is extremely pyrophoric; use with caution; dilute excess in PhMe before quenching with MeOH. The mixture was allowed to stir while warming to 20 °C, then stirred an additional 2 hours. HCl [1.0] (1 mL) was added and the biphasic mixture was extracted with DCM (3 × 2 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (2 mL) and brine (2 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to yield a crude oil. The oil was purified via column chromatography (14 mL SiO₂, 10 – 20% EtOAc/Hexanes) to yield S4 (68.4 mg, 75% yield) as a clear yellow oil. ¹H NMR (499 MHz, CDCl₃) δ 4.56 (t, J = 2.2, 1H), 4.45 (dt, J = 11.5, 6.0, 1H), 3.73 (d, J = 10.4, 1H), 3.65 (d, J = 10.4, 1H), 3.34 (s, 3H), 2.04 (ddd, J = 13.6, 7.0, 2.3, 1H), 1.63 (br s, 1H), 1.55 (dt, J = 9.5, 6.5, 1H), 1.29 (ddd, J = 13.3, 11.0, 2.4, 1H), 0.87 (s, 9H), 0.83 (dd, J = 9.8, 5.8, 1H), 0.69 (t, J = 6.3, 1H), 0.04 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 99.4, 65.6, 60.7, 60.1, 55.7, 34.8, 26.0 (3C), 20.9, 18.5, 11.3, −5.22, −5.24; HRMS (ESI) m/z calcd for C₁₄H₂₈O₄SiNa [M + Na]⁺ 311.1655, found 311.1657.

(±)-(R,R)-Cyclopropylcarbinol 4.10: A sealed 10 mL vial was charged with (±)-(R,R)-dihydropyranol 4.9 (13.7 mg, 0.050 mmol), DCM (0.15 mL) and CH₂I₂ (6.0 μL, 1.5 equiv). The
mixture was cooled to –20 °C before neat Et₂Zn (7.7 μL, 1.5 equiv) was added dropwise via syringe. NOTE: Et₂Zn is extremely pyrophoric; use with caution; dilute excess in PhMe before quenching with MeOH. The mixture was allowed to stir while warming to 20 °C, then stirred an additional 2 hours. HCl [1.0] (1 mL) was added and the biphasic mixture was extracted with DCM (3 × 2 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (2 mL) and brine (2 mL), dried over MgSO₄, filtered, and concentrated in vacuo to yield a crude oil. The oil was purified via column chromatography (SiO₂, 10 – 20% EtOAc/Hexanes) to yield 4.10 (11.7 mg, 82% yield) as a clear yellow oil. 

**1H NMR (500 MHz, CDCl₃) δ**: 4.48 (m, 1H), 4.39 (d, J = 9.0, 1H), 4.02 (d, J = 10.7, 1H), 3.47 (s, 3H), 3.31 (d, J = 10.7, 1H), 2.02 (dd, J = 12.8, 6.9, 1H), 1.71 (br s, 1H), 1.46 (m, 1H), 1.26 (m, 2H), 0.89 (s, 9H), 0.84 (t, J = 6.3, 1H), 0.78 (dd, J = 10.1, 6.1, 1H), 0.06 (s, 3H), 0.05 (s, 3H); **13C NMR (126 MHz, CDCl₃) δ**: 100.8, 66.6, 64.8, 61.7, 56.5, 36.7, 26.0 (3C), 21.9, 18.4, 12.6, –5.17, –5.27; **IR (thin film)** 3383 (br), 2953, 2928, 2857, 1121, 1052, 837 cm⁻¹; **HRMS (ESI) m/z** calcd for C₁₄H₂₈O₄SiNa [M + Na]⁺ 311.1655, found 311.1656.

(±)**-Cyclopropylpyrone S5**: A 10 mL sealed tube was charged with DMSO (42.0 μL, 2.5 equiv), DCM (0.60 mL) and cooled to –78 °C. Oxalyl chloride (31.0 μL, 1.5 equiv) was added dropwise, then stirred for 10 minutes. (±)-(R,S)-cyclopropylcarbinol S4 (68.4 mg, 0.237 mmol) was added dropwise as a solution in DCM (0.30 mL). The mixture was stirred for 0.5 hours, followed by the addition of Et₃N (165 μL, 5 equiv). The mixture was allowed to warm to 20 °C slowly, followed by stirring for an additional 2 hours. The mixture was diluted with DCM (3 mL), washed with H₂O (2 × 3 mL), brine (2 × 3 mL) and dried over MgSO₄. Filtration and concentration in vacuo provided 70
mg of an orange oil which was purified via column chromatography (15 mL SiO₂, 0 – 20% EtOAc/Hexanes) to provide S5 (30.4 mg, 45% yield) as a clear yellow oil. The oil could be stored frozen in benzene, but decomposes after prolonged exposure to room temperature. 

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \] \( \delta \)4.92 (s, 1H), 3.86 (d, \( J = 10.1 \), 1H), 3.74 (d, \( J = 10.2 \), 1H), 3.41 (s, 3H), 2.56 (dd, \( J = 15.4 \), 2.8, 1H), 2.34 (d, \( J = 15.4 \), 1H), 2.01 (dd, \( J = 10.8 \), 6.2, 1H), 1.51 (dd, \( J = 10.9 \), 5.8, 1H), 1.33 (t, \( J = 5.9 \), 1H), 0.85 (s, 9H), 0.04 (s, 6H); 

\[ ^13C \text{ NMR (126 MHz, CDCl}_3 \] \( \delta \)202.2, 102.4, 64.7, 63.6, 55.9, 43.3, 28.3, 25.9 (3C), 21.5, 18.3, –5.34, –5.37; IR (thin film) 2929, 2857, 1718, 838 cm\(^{-1}\); 

LRMS (ESI) \( m/z \) calcd for \( C_{14}H_{26}O_4SiNa \) [M + Na]\(^+\) 309.1498, found 309.1498.

\[ \text{MeO} \]
\[ \text{OTBS} \]
\[ \text{OMe} \]

(±)-Methoxy ketal 4.11: To a 0 °C solution of MeOH (0.10 mL) and \( p \)-TsOH·H\(_2\)O (0.24 mg, 0.05 equiv) was added S5 (7.5 mg, 0.0262 mmol) as a solution in DCM (0.10 mL). The mixture was allowed to stir for 30 min, then sat aq NaHCO\(_3\) (1 mL) was added. The biphasic mixture was extracted with DCM (3 × 1 mL). The combined organic extracts were washed with brine (1 mL) dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo} to give 8 mg of crude. The crude was purified via column chromatography (10 mL SiO₂, 3%EtOAc/PhMe, \( R_f = 0.1 \)) to provide 4.11 as a 1:1 mixture of inseparable diastereomers. (see spectra) HRMS (ESI) \( m/z \) calcd for \( C_{15}H_{30}SiO_5Na \) [M + Na]\(^+\) 341.1760, found 341.1752.

Nitroaldol Experimentalns

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(±)-**Allylic alcohol S6**: A 100 mL round bottom flask was charged with ketone 4.17 (prepared according to Haddad)\(^\text{20}\) (873 mg, 2.50 mmol) and Toluene (17 mL), then cooled to \(-78^\circ\text{C}\). DIBALH (490 μL, 1.1 equiv) was added dropwise via syringe. The color of the mixture was observed to change from clear yellow to clear orange. After stirring for 12 hours starting material was still observed. DIBALH (100 μL) was added and the mixture was stirred for 1 hour. The mixture was warmed to 0 °C, and H\(_2\)O (130 μL) was added. The mixture was stirred, then [4] aqueous NaOH (130 μL) was added, followed by H\(_2\)O (380 μL). The mixture was dried over Na\(_2\)SO\(_4\), filtered through celite and concentrated *in vacuo*. The crude oil (930 mg) was purified via column chromatography (150 mL SiO\(_2\), 500 mL 5% EtOAc/Hex, \(R_f = 0.1\)) to yield S6 (607 mg, 69% yield). \(^1\text{H} \text{NMR} \text{(499 MHz, CDCl}_3\text{)} \delta 6.68 \text{ (s, 1H), 4.39 (ddd, } J = 11.4, 3.8, 0.8, \text{1H), 4.30 (br s, 1H), 4.16 (ddd, } J = 11.9, 11.0, 2.7, \text{1H), 2.26 (d, } J = 2.8, \text{1H), 2.13–2.20 (m, 1H), 2.06–2.11 (m, 1H), ; } ^{13}\text{C} \text{NMR (126 MHz, CDCl}_3\text{)} \delta 150.3, 98.5, 66.1, 63.9, 34.7, 31.7; \text{ IR (thin film) 3400, 2977, 2927, 1069, 1018 cm}^{-1}.\)

(±)-**TBS ether 4.19**: A sealed vial was charged with allylic alcohol S6 (593 mg, 1.69 mmol), DCM (3.4 mL) and imidazole (345 mg, 3.0 equiv). TBSCl (383 mg, 1.5 equiv) was added in one portion by removing the septum and adding in one portion. The mixture was allowed to stir for 12 hours. The mixture was poured over saturated aqueous NaHCO\(_3\) (3 mL) and extracted with Et\(_2\)O (3 × 3
The combined organic extracts were washed with brine (3 mL), dried over MgSO₄, and concentrated in vacuo to provide a yellow oil (840 mg). The oil was purified via column chromatography (70 mL SiO₂, 0–5% EtOAc/Hexanes, Rₜ = 0.45 at 5% EtOAc/Hexanes) to provide 4.19 (711 mg, 90% yield) as a clear oil. ^1^H NMR (500 MHz, CDCl₃) δ 6.73 (s, 1H), 4.36 (d, J = 3.6, 1H), 4.25 (s, 1H), 4.19 (app t, J = 12.4, 1H), 2.11 (ddt, J = 13.7, 12.9, 3.9, 1H), 1.91 (dd, J = 14.2, 2.1, 1H), 0.91 (s, 9H), 0.17 (s, 3H), 0.11 (s, 3H); ^1^C NMR (126 MHz, CDCl₃) δ 149.5, 99.1, 66.9, 63.7, 35.3, 33.6, 25.9 (3C), 18.2, −4.2, −4.5; IR (thin film) 3041, 2954, 2930, 2886, 2857, 1260, 835 cm⁻¹; HRMS (ESI) m/z calcd for C₁₂H₂₁Br₃O₂SiNa [M + Na]⁺ 484.8759, found 484.8779.

(±)-Aldehyde 4.20: A 50 mL round bottom flask was charged with gem-dibromide 4.19 (508 mg, 1.09 mmol), acetone (750 μL), H₂O (250 μL), and AgTFA (482 mg, 2.0 equiv). The heterogeneous mixture was stirred for 12 hours at 20 °C. The mixture was filtered through a pad of celite and the pad was rinsed with EtOAc. The aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (3 mL), dried over MgSO₄, and concentrated in vacuo to provide a yellow oil (335 mg). The crude was purified via column chromatography (80 mL SiO₂, 3–5% EtOAc/Hexanes) to provide 4.20 (198 mg, 56% yield). ^1^H NMR (500 MHz, CDCl₃) δ 9.88 (s, 1H), 4.35 (s, 1H), 4.27 (d, J = 10.8, 1H), 4.09 (td, J = 12.0, 1.8, 1H), 2.05–2.12 (m, 1H), 1.94 (dd, J = 14.3, 2.1, 1H), 0.90 (s, 9H), 0.20 (s, 3H), 0.13 (s, 3H); ^1^C NMR (126 MHz, CDCl₃) δ 186.8, 146.6, 118.7, 67.7, 62.5, 33.2, 25.8 (3C), 18.1, −4.3, −4.5; IR (thin film) 2928, 2856, 1701, 1090, 833 cm⁻¹; LRMS (ESI) m/z calcd for C₁₂H₂₁O₃⁷⁹BrSiNa [M + Na]⁺ 343.0341, found 343.0324.
(±)-Nitro alcohol 4.21: A 25 mL round bottom flask was charged with nitroethane (43.0 μL, 1.5 equiv) and THF (4 mL) then cooled to –78 °C. n-BuLi (480 μL of [2.5] in hexanes, 3.0 equiv) was added dropwise via syringe and the mixture was stirred for 15 min. Aldehyde 4.20 (128 mg, 0.400 mmol) was added dropwise via syringe as a solution in THF (1 mL) and the mixture was stirred for 3 hours before being warmed to 0 °C. The cooling bath was removed and Et₂O (2 mL) and H₂O (2 mL) were added and the biphasic mixture was extracted with Et₂O (6 × 3mL). The combined organic extracts were washed with brine (3 mL), dried over MgSO₄, and concentrated in vacuo to provide a crude oil (155 mg). The crude was composed of a mixture of four diastereomeric products, two of which could be separated easily from the others via column chromatography (80 mL SiO₂, 10% EtOAc/Hexanes). Data for diastereomer “A”: R_f = 0.40 in 20% EtOAc/Hexanes; 39.7 mg, 25% yield; ¹H NMR (500 MHz, CDCl₃) δ 5.11 (t, J = 8.4, 1H), 4.78 (ddd, J = 14.7, 8.1, 6.9, 1H), 4.25 (s, 1H), 4.20 (dt, J = 10.7, 3.0, 1H), 4.09 (td, J = 12.7, 2.0, 1H), 2.6 (d, J = 8.3, 1H), 1.99 (tt, J = 14.3, 3.9, 1H), 1.90 (dd, J = 14.3, 2.6, 1H), 1.53 (d, J = 6.8, 3H), 0.91 (s, 9H), 0.18 (s, 3H), 0.12 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 148.5, 103.1, 85.9, 72.5, 66.6, 62.9, 33.5, 25.9 (3C), 18.2, 15.9, –4.2, –4.5; IR (thin film) 3494, 2955, 2930, 2888, 2857, 1555, 1083, 833 cm⁻¹; HRMS (ESI) m/z calcd for C₁₄H₂₆⁷⁹BrO₃NSiNa [M + Na]⁺ 418.0661, found 418.0646. Data for diastereomer “B”: R_f = 0.38 in 20% EtOAc/Hexanes; 25.5 mg, 16% yield; spectra attached.

Oxime Anion Experimental
(E)-Oxime 4.48: A 10 mL open vial was charged with 1-((tert-butyldimethylsilyl)oxy)propan-2-one (prepared according to literature precedent)\textsuperscript{51} (838 mg, 4.45 mmol), K$_2$CO$_3$ (369 mg, 0.6 equiv) and H$_2$O (2.2 mL). The mixture was vigorously stirred while H$_2$NOH•HCl (402 mg, 1.3 equiv) was added in one portion. Effervescence was observed and the mixture was stirred for two hours when no starting material was observed by TLC. The aqueous mixture was extracted with DCM (3 × 1 mL) and the combined organic extracts were dried over MgSO$_4$. The crude contained a 1.0 : 1.37 ratio of Z : E oxime isomers, which could be separated via flash column chromatography (SiO$_2$, 10% EtOAc/Hexanes); TLC (10% EtOAc/Hexanes) E isomer R$_f$ = 0.18, Z isomer R$_f$ = 0.13. E oxime 4.48 was isolated (427 mg) in 47% yield and Z oxime (109 mg) in 12% yield. Data for E isomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.85 (s, 1H), 4.15 (s, 2H), 1.91 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 157.7, 65.0, 25.9 (3C), 18.4, 11.1, -5.3 (2C); IR (thin film) 3246 (br), 2955, 2930, 2858, 1471, 1257, 1102, 839 cm$^{-1}$; LRMS (ESI) $m/z$ calcd for C$_9$H$_{21}$NO$_2$SiNa [M + Na]$^+$ 226.1239, found 226.1116. Data for Z isomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.05 (s, 1H), 4.54 (s, 2H), 1.92 (s, 3H), 0.91 (s, 9H), 0.08 (2s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 160.8, 59.1, 25.9 (3C), 16.5, -5.4 (2C).

Cyclic vinylogous carbonate 4.36: A 25 mL round bottom flask was charged with paraformaldehyde (30.0 mg, 1.0 equiv), and DCM (3.8 mL) and cooled to −78 °C. Et$_2$AlCl (1.08 mL, 1.1 equiv) was added dropwise via syringe, followed by neat Brassard’s diene\textsuperscript{52} (500 mg, 2.17
mmol). In the course of stirring for 30 minutes, the solution turned from clear to yellow. The cooling bath was replaced with an ice bath. In the course of stirring for 30 minutes the solution turned from yellow to red. The ice bath was removed and the solution stirred for 1 hour. H₂O (3 mL) was added and the aqueous phase was extracted with Et₂O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried over MgSO₄ and concentrated in vacuo. The crude was purified via column chromatography (SiO₂, 30% EtOAc/Hexanes, Rₚ = 0.23 in 50% EtOAc/Hexanes) to provide 4.36 (60 mg, 43% yield) as a yellow solid. ¹H NMR (600 MHz, CDCl₃) δ 5.07 (s, 1H), 4.31 (t, J = 6.5, 2H), 3.92 (q, J = 7.0, 2H), 2.48 (t, J = 6.5, 2H), 1.34 (t, J = 7.3, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 172.4, 167.2, 90.8, 64.8, 64.5, 27.9, 14.0; IR (thin film) 2985, 2942, 2902, 1703, 1619, 1218, 1085, 920, 818; LRMS (ESI) m/z calcd for C₇H₁₀O₃Na [M + Na]⁺ 165.0528 and C₁₄H₂₀O₆Na [2M + Na]⁺ 307.1158, found 165.0369 and 307.0858.

Ethyl ether 4.49: A sealed tube was charged with i-Pr₂NH (360 μL, 2.4 equiv), THF (1 mL) and cooled to −78 °C. n-BuLi (1.03 mL of [2.5] in hexanes, 2.4 equiv) was added dropwise and the mixture was stirred for 10 minutes. Acetone oxime 4.47 (93.8 mg, 1.2 equiv) was added as a solution in THF (1 mL) dropwise via syringe. A solid precipitate forms (mono-deprotonated) and the cooling bath was removed. Upon warming the precipitate dissolved with stirring; stir 1 hour at 20 °C. The −78 °C bath was replaced, then cyclic vinylogous carbonate 4.36 (152 mg, 1.07 mmol) was added as a solution in THF (1 mL) via syringe. In the course of stirring over 30 minutes the solution turned bright red. The cooling bath was removed and the mixture stirred for 30 minutes. Et₂O (5 mL) and [1] HCl was added until the solution color changes to light yellow. The aqueous phase was extracted.
with Et₂O (3 × 3 mL). The combined organic extracts were washed with brine (3 mL), dried over MgSO₄, and concentrated in vacuo to yield a yellow oil (110 mg), which was purified via column chromatography (SiO₂, 50% EtOAc/Hexanes, Rf = 0.66 in 80% EtOAc/Hexanes) to afford 4.49 (22 mg, 10% yield) as an oil. ¹H NMR (500 MHz, C₆D₆) δ 5.65 (s, 1H), 5.34 (s, 1H), 3.71 (t, J = 5.6, 2H), 3.20 (q, J = 6.2, 2H), 2.68 (t, J = 6.6, 2H), 2.00 (s, 3H), 0.91 (t, J = 6.3, 3H); ¹³C NMR (126 MHz, C₆D₆) δ 168.6, 162.0, 159.6, 100.9, 89.7, 63.4, 60.4, 36.3, 14.1, 11.2; IR (thin film) 3389, 2981, 2935, 2886, 1645 cm⁻¹; HRMS (ESI) m/z calcd for C₁₀H₁₅NO₃Na [M + Na]⁺ 220.0950, found 220.0941.

**Vinylogous diketone 4.51:** An open vial was charged with ethyl ether 4.49 (20.0 mg, 0.101 mmol), PhH (2 mL), H₂O (10 μL, 5.5 equiv) and p-TsOH·H₂O (1.8 mg, 0.09 equiv). The homogenous mixture was slow to form product by TLC after stirring for 6 hours at 20 °C. The mixture was warmed to 50 °C and stirred until no product was observed by TLC, 2 hours. The mixture was concentrated and purified via column chromatography (15 mL SiO₂, 80% EtOAc/Hexanes, Rf = 0.22) to afford 4.51 (7.7 mg, 60% yield). ¹H NMR (500 MHz, C₆D₆) δ 5.58 (s, 1H), 3.45 (t, J = 4.8, 2H), 3.13 (s, 2H), 1.99 (t, J = 5.6, 2H), 1.90 (s, 3H); ¹³C NMR (126 MHz, C₆D₆) δ 202.9, 165.2, 159.8, 104.1, 57.6, 44.4, 40.6, 11.1; IR (thin film) 3402, 2929, 1721, 1609, 1422, 1051 cm⁻¹; HRMS (ESI) m/z calcd for C₈H₁₁NO₃Na [M + Na]⁺ 192.0637, found 192.0636.
**Oxime 4.58:** A sealed tube was charged with oxime 4.51 (4.1 mg, 0.0242 mmol), CH$_3$I (2.9 μL, 1.5 equiv) and DCM (240 μL) then cooled to –20 °C. Et$_2$Zn (3.7 μL, 1.5 equiv) was added via syringe and a white precipitate was observed to form on the sides of the reaction flask. The cooling bath was removed and the mixture allowed to stir for 1 hour. DCM (1 mL) and [1] aq. HCl (2mL) was added to the flask and the aqueous phase was extracted with DCM (3 × 1 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over MgSO$_4$, and concentrated *in vacuo*. The crude was purified via column chromatography (15 mL SiO$_2$, 80% EtOAc/Hexanes, $R_f = 0.22$) to afford 4.58 (4.0 mg, 90% yield) with starting material as a 16% impurity. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.84 (s, 1H), 3.87 (t, $J = 5.0$, 2H), 3.01 (t, $J = 6.9$, 2H), 2.87 (t, $J = 6.8$, 2H), 2.70 (t, $J = 5.1$, 2H), 2.25 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 209.0, 171.5, 160.0, 102.2, 57.9, 44.6, 40.5, 20.6, 11.6; IR (thin film) 3390, 2925, 1717, 1049 cm$^{-1}$; LRMS (ESI) m/z calcd for C$_9$H$_{13}$NO$_3$Na [M + Na]$^+$ 206.08, found 206.10 and C$_9$H$_{14}$NO$_3$ [M + H]$^+$ 184.10, found 184.12.

**Ketene Diels–Alder**

![Ketene Diels–Alder](image)

**Dioxinone ester 4.66:** A 1 L round bottom flask was charged with THF (450 mL), Et$_3$N (1.90 mL, 0.1 equiv) and cooled to –78 °C. Ethyl oxalyl chloride (16.6 mL, 1.1 equiv) was added via syringe, followed by silyl diene 4.65 (prepared according to a procedure by Carreira)$^{53}$ (28.9 g, 135 mmol) neat via syringe, dropwise over 5 minutes. The solution was stirred for 5 minutes and was observed turning yellow. The cooling bath was removed and stirring was continued for 90 minutes. Et$_2$O (200 mL) was added followed by [1] aq. HCl (50 mL). The biphasic mixture was shaken, separated, and
the aqueous phase was extracted with Et$_2$O (100 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over MgSO$_4$, and concentrated in vacuo to provide a yellow solid. The crude was solubilized in a minimal amount of EtOAc. Hexanes were added to crash out a white solid, which was filtered and rinsed with hexanes. The white solid was dried in vacuo to provide **4.66** (12.0 g, 37% yield). $^1$H NMR (499 MHz, C$_6$D$_6$) δ 6.59 (s, 1 H), 5.89 (s, 1H), 3.86 (q, $J$ = 7.2, 2H), 1.3 (s, 6H), 0.87 (t, $J$ = 7.1, 3H), $^{13}$C NMR (126 MHz, C$_6$D$_6$) 163.4, 163.2, 162.6, 149.0, 106.1, 101.5, 97.3, 62.9, 24.7 (2C), 13.8; IR (thin film) 2991, 1723, 1249, 1015 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{11}$H$_{14}$O$_6$Na [M + Na]$^+$ 265.0688, found 265.0692.

Dioxinone oxime **4.72**: A 250 mL round bottom flask was charged with dioxinone ester **4.71** (3.31 g, 13.7 mmol), EtOH (68 mL) and H$_2$NOH·HCl (1.14 g, 1.2 equiv). The mixture was stirred for 1 hour, then sat. aq. NaHCO$_3$ (20 mL) was added and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (10 mL), dried with MgSO$_4$, and concentrated in vacuo to provide a yellow oil that consisted primarily of the spirocyclic product **4.73**. The yellow oil was taken up in DCM (24 mL) in a 100 mL round bottom flask, to which imidazole (1.48 g, 3.0 equiv) and TBSCl (1.65 g, 1.5 equiv) were added. After 2 hours of stirring sat. aq. NaHCO$_3$ (20 mL) was added and the biphasic mixture was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO$_4$, and concentrated in vacuo to provide a brown oil. The crude was purified via column chromatography (SiO$_2$, 5% EtOAc/Hexanes, $R_f$ = 0.15) to provide **4.72** (2.64 g, 52% yield) as a yellow oil.
Alternative procedure: A 1 L round bottom flask was charged with dioxinone ester 4.71 (12.0 g, 49.5 mmol) and DCM (100 mL). \( O-(\text{tert-butyl} \text{dimethyl}silyl)\text{hydroxylamine} \) was added to the flask in one portion and the mixture was stirred for 2 hours. After 30 minutes of stirring a precipitate had formed in solution. Sat. aq. \( \text{NaHCO}_3 \) (20 mL) was added to the flask and the biphasic mixture was extracted with DCM (3 × 30 mL). The combined organics were washed with brine (20 mL), dried with \( \text{MgSO}_4 \) and concentrated \textit{in vacuo} to provide an intermediate, which by NMR was neither product nor starting material; it was postulated that this intermediate was the hemiaminal. The crude was taken in DCM (100 mL) and treated with imidazole (5.05 g, 1.5 equiv), TBSCl (7.47 g, 1.0 equiv) and stirred for 12 hours. Sat. aq. \( \text{NaHCO}_3 \) (20 mL) was added to the flask and the biphasic mixture was extracted with DCM (3 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried over \( \text{MgSO}_4 \) and concentrated \textit{in vacuo} to provide 25 grams of a yellow oil that consists of a mixture of product and TBS protected starting material. The crude was purified via flash column chromatography (800 mL SiO\(_2\), 5 – 10 % EtOAc/Hexanes) to provide 4.72 as a clear oil (7.37 g, 40% yield). \(^1\)H NMR (500 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta \) 5.30 (s, 1H), 3.94 (q, \( J = 7.2, 2H \)), 3.36 (s, 2H), 1.27 (s, 6H), 0.94 (s, 9H), 0.90 (t, \( J = 7.2, 3H \)), 0.17 (s, 6H); \(^{13}\)C NMR (126 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta \) 165.6, 163.2, 159.7, 151.1, 106.5, 95.1, 61.8, 29.7, 25.9 (3C), 24.7 (2C), 18.2, 14.0, –5.2 (2C); IR (thin film) 2933, 2859, 1736, 1204, 842 cm\(^{-1}\); HRMS (ESI) \( m/z \) calcd for \( \text{C}_{17}\text{H}_{29}\text{NO}_{6}\text{SiNa} [\text{M} + \text{Na}]^+ \) 394.1662, found 394.1658.
**Dihydropyrene 4.74:** A 100 mL 3-neck round bottom flask was fitted with a condenser and charged with n-butylvinyl ether (15.8 mL, 20.0 equiv), then heated to reflux. Dioxinone 4.72 (2.27 g, 6.11 mmol) was added dropwise as a solution in PhMe (2 mL). Stirring was continued for 30 minutes then the heating bath was removed. The mixture was concentrated in vacuo and purified via column chromatography (100 mL SiO$_2$, 10% EtOAc/Hexanes) to provide 4.74 (1.24 g, 49% yield). $^1$H NMR (600 MHz, C$_6$D$_6$) $\delta$ 5.55 (s, 1H), 4.78 (dd, $J = 5.1$, 3.9, 1H), 3.98 (qd, $J = 7.2$, 2.7, 2H), 3.65 (dt, $J = 9.4$, 6.6, 1H), 3.58 (d, $J = 15.0$, 1H), 3.53 (d, $J = 15.0$, 1H), 3.16 (dt, $J = 9.4$, 6.6, 1H), 2.44 (dd, $J = 16.6$, 5.2, 1H), 2.34 (dd, $J = 16.5$, 3.9, 1H), 1.39 (quin, $J = 6.8$, 2H), 1.24 (app sex, $J = 7.5$, 2H), 0.97 (s, 9H), 0.93 (t, $J = 7.2$, 3H), 0.92 (t, $J = 7.3$, 3H), 0.21 (s, 6H); $^{13}$C NMR (126 MHz, C$_6$D$_6$) $\delta$ 189.1, 166.6, 163.5, 152.0, 106.0, 102.2, 69.3, 61.7, 31.7, 30.7, 26.0 (3C), 18.3, 14.03, 13.95, –5.14, –5.15; IR (thin film) 2958, 2860, 1714, 842 cm$^{-1}$; HRMS (ESI) $m/z$ calcd for C$_{21}$H$_{37}$NO$_6$SiNa [M + Na]$^+$ 450.2288, found 450.2296.

![Chemical structure](image)

**Allylic alcohol 4.81:** A 50 mL round bottom flask was charged with dihydropyrene 4.74 (449 mg, 1.09 mmol) and THF (10.9 mL) then cooled to –30 °C. LiBH$_4$ [2.0] in THF (542 μL, 1.0 equiv) was added dropwise; upon addition of LiBH$_4$ the mixture was observed turning light yellow. After 3 hours of stirring the mixture was allowed to warm to 10 °C then EtOAc (10 mL) was added followed by sat. aq. NH$_4$Cl (5 mL). The biphasic mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO$_4$, and concentrated in vacuo to provide 561 mg of a crude oil. The crude was purified via flash column chromatography.
(SiO₂, 10% EtOAc/Hexanes) to provide 4.81 (218 mg, 48% yield). ¹H NMR (500 MHz, C₆D₆) δ 5.20 (d, J = 5.2, 1H), 4.83 (s, 1H), 4.05–3.98 (m, 2H), 3.97–3.92 (m, 1H), 3.68–3.63 (m, 1H), 3.63 (d, J = 10.9, 1H), 3.14 (dt, J = 9.4, 6.5, 1H), 3.03 (d, J = 11.6, 1H) 2.01 (dd, J = 14.3, 1.4, 1H), 1.57 (ddd, J = 14.3, 5.0, 2.7, 1H), 1.37–1.33 (m, 2H), 1.24 (app sex, J = 7.4, 2H), 1.01 (s, 9H), 0.95 (t, J = 7.2, 3H), 0.82 (t, J = 7.3, 3H), 0.25 (s, 3H), 0.24 (s, 3H); ¹³C NMR (126 MHz, C₆D₆) δ 163.8, 154.0, 146.5, 103.5, 97.9, 68.7, 61.4, 59.7, 34.8, 31.9, 30.1, 26.1 (3C), 19.6, 18.3, 14.1, 14.0, –5.07 (2C); IR (thin film) 3562, 2933, 2859, 1723, 850 cm⁻¹; HRMS (ESI) m/z calcd for C₂₀H₃₇NO₆SiNa [M + Na]⁺ 438.2288, found 438.2280.

Cyclopropylcarbinol S7: A 100 mL round bottom flask was charged with allylic alcohol 4.81 (contains 2,2,6-trimethyl-4H-1,3-dioxin-4-one as a 41% impurity) (200 mg, 0.283 mmol), CH₂I₂ (58.0 μL, 1.5 equiv) and DCM (4.80 mL) then cooled to –30 °C. Et₂Zn (58.0 μL, 1.1 equiv) was added dropwise, then the reaction mixture was allowed to warm to 22 °C and stir for an additional 1 hour. [1] HCl (1 mL) was added to the flask and the biphasic mixture was extracted with DCM (3 × 3 mL). The combined organic extracts were washed with brine (3 mL), dried over MgSO₄ and concentrated in vacuo to provide a yellow oil. The crude was purified via flash column chromatography (SiO₂, 10 – 20% EtOAc/Hexanes) to provide S7 (65 mg, 63% yield based on purity of starting material) as a yellow oil. ¹H NMR (500 MHz, C₆D₆) δ 4.32 (d, J = 8.7, 1H), 4.24–4.20 (m, 1H), 4.09–4.00 (m, 2H), 3.95 (dt, J = 9.5, 6.5, 1H), 3.37 (dt, J = 9.5, 6.5, 1H), 3.22 (d, J = 13.0, 1H), 2.87 (d, J = 13.0, 1H), 1.92 (dd, J = 12.9, 6.7, 1H), 1.56–1.50 (m, 2H), 1.40–1.25 (m, 4H), 1.04 (dd,
1H = 13.5, 6.8, 1H), 1.01 (s, 9H), 0.98 (t, $J = 7.5$, 3H), 0.86 (t, $J = 7.4$, 3H), 0.81 (t, $J = 6.3$, 1H), 0.64 (dd, $J = 10.1$, 6.0, 1H), 0.24 (s, 3H), 0.23 (s, 3H); $^{13}$C NMR (126 MHz, C$_6$D$_6$) δ 164.7, 155.6, 99.2, 68.6, 64.3, 61.4, 58.9, 37.0, 32.7, 32.2, 26.2 (3C), 25.0, 19.8, 18.4, 15.7, 14.10, 14.09, –4.97, –5.00; IR (thin film) 3423, 2959, 2933, 1724, 841 cm$^{-1}$; HRMS (Cl) $m/z$ calcd for C$_{21}$H$_{39}$NO$_6$SiH [M + H]$^+$ 430.2652, found 430.2617.

![Donor acceptor cyclopropane 4.75](image)

**Donor acceptor cyclopropane 4.75:** A 100 mL round bottom flask was charged with DCM (4.10 mL) and oxalyl chloride (105 μL, 1.5 equiv) then cooled to –78 °C. DMSO (145 μL, 2.5 equiv) was added dropwise and the mixture was stirred for 15 minutes. Cyclopropylcarbinol S7 (352 mg, 0.819 mmol) was added as a solution in DCM (1 mL). The solution yellows over the course of stirring for 15 minutes. Et$_3$N (457 μL, 4.0 equiv) was added slowly and the mixture was allowed to warm to 20 °C. Over the course of stirring for 10 minutes the solution turned purple. H$_2$O (2 mL) was added and the biphasic mixture was extracted with DCM (3 × 3 mL). The combined organic extracts were washed with brine (3 mL), dried over MgSO$_4$, and concentrated in vacuo. The crude was purified via flash column chromatography (30 mL SiO$_2$, 10% EtOAc/Hexanes) to provide 4.75 (265 mg, 90% purity, 76% yield) as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 4.78 (dd, $J = 8.3$, 2.7, 1H), 4.30–4.25 (m, 2H), 3.81 (dt, $J = 9.5$, 6.5, 1H), 3.39 (dt, $J = 9.5$, 6.6, 1H), 3.11 (d, $J = 13.2$, 1H), 3.07 (d, $J = 13.2$, 1H), 2.47 (dd, $J = 16.6$, 1.6, 1H), 2.32 (dd, $J = 16.6$, 8.3, 1H), 1.86, (dd, $J = 11.4$, 6.3, 1H), 1.57–1.50 (m, 3H), 1.39–1.35 (m, 3H), 1.33 (t, $J = 7.1$, 3H), 0.94 (s, 9H), 0.91 (t, $J = 7.4$, 3H), 0.22 (s, 3H), 0.21 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 204.3, 164.4, 153.3, 100.1, 69.1, 61.8, 61.3,
44.7, 31.7, 31.1, 30.8, 26.1 (3C), 23.5, 19.4, 18.3, 14.2, 14.0, –5.06 (2C); IR (thin film) 2958, 2933, 2860, 1714, 842 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd for C\(_{21}\)H\(_{37}\)NO\(_6\)SiNa [M + Na]\(^+\) 450.2288, found 450.2296.

**Oxime S8:** A 25 mL round bottom flask was charged with cyclopropylcarbinol S7 (47 mg, 0.109 mmol) and EtOH (1.1 mL). CSA (5.08 mg, 0.2 equiv) was added in one portion and the mixture was allowed to stir until the starting material was fully consumed by TLC. Sat. aq. NaHCO\(_3\) was added and the mixture was extracted with Et\(_2\)O (3 × 3 mL). The combined organic extracts were dried over MgSO\(_4\) and concentrated in vacuo. The crude was purified via flash column chromatography (SiO\(_2\), 50% EtOAc/Hexanes, \(R_f = 0.16\)) to provide S8 (15.0 mg, 43% yield). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\) 10.41 (br s, 1H), 4.30–4.25 (m, 2H), 4.09–4.03 (m, 2H), 3.97 (dt, \(J = 9.4, 6.6, 1H\)), 3.39 (dt, \(J = 9.4, 6.6, 1H\)), 3.18 (d, \(J = 12.9, 1H\)), 2.82 (d, \(J = 13.0, 1H\)), 1.97 (dd, \(J = 12.5, 6.7, 2H\)), 1.58–1.53 (m, 2H), 1.42–1.36 (m, 3H), 1.36–1.27 (m, 2H), 1.03 (t, \(J = 7.1, 3H\)), 0.88 (t, \(J = 7.4, 3H\)), 0.70 (dd, \(J = 10.2, 6.0, 1H\)); \(^{13}\)C NMR (126 MHz, C\(_6\)D\(_6\)) \(\delta\) 164.4, 150.6, 99.5, 68.9, 65.0, 61.8, 59.1, 36.8, 32.2, 32.1, 24.9, 19.7, 16.2, 14.15, 14.14; IR (thin film) 3291 (br), 3068, 2960, 2928, 2873, 1722, 1042 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd for C\(_{13}\)H\(_{25}\)NO\(_6\)Na [M + Na]\(^+\) 338.1580, found 338.1573.
**5,7-Spirocylce 4.82**: To a 10 mL glass test tube was added cyclopropylcarbinol S7 (67.0 mg, 0.212 mmol) and DCM (2.3 mL). PCC (101.7 mg, 2.22 equiv) was added in one portion to the flask. The mixture was stirred for 45 minutes, then filtered through a plug of SiO₂ and rinsed with EtOAc (2 × 2 mL). The organic extracts were dried *in vacuo* and purified via flash column chromatography (SiO₂, 20 – 50% EtOAc/Hexanes, product R₂ = 0.46 in 50% EtOAc/Hexanes) to provide recovered starting material (15.9 mg, 24% recovered) and 4.82 (16.0 mg, 24% yield) as a 1.0 : 0.86 mixture of diastereomers. NMR characterization (spectra attached) were complicated by the presence of two diastereomers. IR (thin film) 2959, 2934, 2873, 2360, 2340, 1717, 1125 cm⁻¹; HRMS (ESI) m/z calcd for C₁₅H₂₃NO₆Na [M + Na]⁺ 336.1423, found 336.1424.

![Spirocyclic structure](image)

**α,β-Unsaturated oxime 4.80**: To a 10 mL glass test tube was added spirocycle 4.82 (3.8 mg, 0.0121 mmol), benzene (1.0 mL) and the mixture was brought to 40 °C. p-TsOH•H₂O (1.2 mg, 0.5 equiv) was added in one portion and the mixture was stirred for 30 minutes. Sat. aq. NaHCO₃ (1 mL) was added and the biphasic mixture was extracted with EtOAc (3 × 1 mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Purification via SiO₂ chromatography results in decomposition of 4.80 as observed by 2D TLC. Purification via flash column chromatography (SiO₂, 33 – 50% EtOAc/Hexanes) provided 4.80 (1.2 mg, 40% yield, 80% purity). ¹H NMR (500 MHz, C₆D₆) δ 7.05 (d, J = 4.7, 1H), 6.10 (s, 1H), 4.71 (d, J = 4.7, 1H), 4.03 (q, J = 7.2, 2H), 2.45 (t, J = 7.6, 2H), 1.93 (t, J = 7.5, 2H), 0.94 (t, J = 7.1, 3H); ¹³C NMR (126 MHz, C₆D₆) δ 198.5, 173.5, 172.3, 160.4, 157.0, 102.2, 101.7, 61.8, 36.8, 21.2, 14.0; HRMS (ESI) m/z calcd for C₁₁H₁₃NO₅Na [M + Na]⁺ 262.0692, found 262.0699.
Alcohol 4.88: A 10 mL cylindrical flask was charged with dioxinone 4.72 (31.2 mg, 0.0840 mmol) and THF (280 μL) then cooled to –78 °C. KHMDS [0.5] in toluene (168 μL, 1.0 equiv) was added dropwise and the mixture was stirred for 30 minutes. TMSCl (11 μL, 1.0 equiv) was added and the mixture was allowed to warm to 22 °C. The mixture was concentrated in vacuo and taken in C₆D₆ (300 μL). NMR analysis of the crude indicates a ratio of 1.0:0.57 of the dienoxysilane 4.87 to 4.72 with trace amounts of impurities. DCM (300 μL) and mCPBA (8.7 mg, 0.6 equiv) was added to the mixture, which was stirred for 1 hour. The reaction mixture was concentrated in vacuo and purified via flash column chromatography (SiO₂, 20% EtOAc/Hexanes) to provide 4.88 (7.0 mg, 21% yield).

Structural assignment was assisted by comparing spectra to a similar known dioxinone (compound 4c in reference).³⁸ ¹H NMR (500 MHz, C₆D₆) δ 5.84 (s, 1H), 5.81 (d, J = 11.2, 1H), 4.02 (d, J = 11.3, 1H), 3.83 (q, J = 7.1, 2H), 1.27 (s, 3H), 1.24 (s, 3H), 0.87 (s, 9H), 0.81 (t, J = 7.1, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ¹³C NMR (126 MHz, C₆D₆) δ 168.2, 163.3, 159.7, 153.0, 107.0, 93.8, 65.5, 62.1, 25.8 (3C), 24.63, 24.56, 18.2, 13.8, −5.36, −5.39; IR (thin film) 3484 (br), 2928, 2857, 1724, 843 cm⁻¹; LRMS (ESI) m/z calcd for C₁₇H₂₉NO₇SiNa [M + Na]⁺ 410.1611, found 410.0987.

4.8 References


APPENDIX: NMR spectra and GC traces
+ ca. 3%
2.42
+ ca. 5%

[Chemical structures with peaks at 22.77, 26.26, 28.96, 29.27, 29.43, 31.93, 35.26, 60.28, 67.14, 76.91, 77.16, 77.41, 14.23, 172, 194.99]
4.21
Diastereomer A
Diastereomer B
4.21
Diastereomer B

[Chemical structure diagram]
(Z)-4.48
\[
\begin{align*}
\text{H} & \quad 4.51 \\
\text{O} & \quad 165.18 \\
\text{N} & \quad 159.77 \\
\end{align*}
\]
ghmbc optimised for 10 Hz couplings
Data File C:\HPChem2\DATA\WJC\WJC51279.D

Sample Name: WJC-V-127-1

CHIRALDEX B, 30 psi, 145 C

Injection Date : 12/21/13 1:08:31 PM
Sample Name : WJC-V-127-1
Acq. Operator : WJC

Acq. Method : C:\HPChem2\METHODS\RIGHT.M
Last changed : 12/21/13 1:07:03 PM by WJC
(modified after loading)
Analysis Method : C:\HPChem2\METHODS\RIGHT.M
Last changed : 12/21/13 1:32:58 PM by WJC
(modified after loading)

Injection Volume : Manually

Checkout of Right 5890 GC, oven at 39'C, Fid on. Zones on.
ADC1 B, ADC1 Right CHANNEL B (WJCWJC51279.D)

(-)-2.19
98:2 d.r.

---

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: ADC1 B, ADC1 Right CHANNEL B

<table>
<thead>
<tr>
<th>Peak</th>
<th>Ret.Time</th>
<th>Width</th>
<th>Area [min]</th>
<th>[min] [pa*sec]</th>
<th>[pa]</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.601</td>
<td>0.133</td>
<td>1.99261e4</td>
<td>2490.71655</td>
<td>2.75046</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>16.578</td>
<td>0.136</td>
<td>7.04536e5</td>
<td>8.58330e4</td>
<td>97.24954</td>
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</tr>
</tbody>
</table>

Totals : 7.24463e5 8.83237e4

Results obtained with enhanced integrator:

*** End of Report ***

Right GC 2 12/21/13 1:33:25 PM WJC
Data File C:\HPChem\2\DATA\WJC\RACDNA3.D
Sample Name: rac-danalipino

CHIRALDEX B, 145 C, 30 psi
rac-vinyl epoxide for danicalipin A

Injection Date: 5/13/13 8:17:54 PM
Sample Name: rac-danicalipin
Location: Vial 1
Acq. Operator: WJC
Inj Volume: Manually

Acq. Method: C:\HPChem\2\METHODS\RIGHT.M
Last changed: 5/13/13 8:36:43 PM by WJC
(modified after loading)
Analysis Method: C:\HPChem\2\METHODS\RIGHT.M
Last changed: 5/13/13 8:36:43 PM by WJC
(modified after loading)

Checkout of Right 5890 GC, oven at 39°C, Fid on. Zones on.

ADC1 B, ADC1 Right CHANNEL B (WJC\RACDNA3.D)

Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000

Signal 1: ADC1 B, ADC1 Right CHANNEL B

Peak RetTime Type Width Area Height Area
# [min] [min] [pa*s] [pa] %
---|-----|------|--------|---------|
1 15.700 MM 0.1273 1.01638e5 1.33040e4 50.05713
2 16.758 MM 0.1366 1.01406e5 1.23741e4 49.94287

Totals: 2.03044e5 2.56782e4

Results obtained with enhanced integrator!

*** End of Report ***

Right GC 2 5/13/13 8:39:37 PM WJC
Data File C:\HPCHM\2\DATA\WJC\WJCS1274.D
Sample Name: WJC-V-127-2
CHIRALDEX B, 30 psi, 165 C

Injection Date : 6/17/13 6:53:22 PM
Sample Name : WJC-V-127-2 Location : Vial 1
Acq. Operator : WJC Inj Volume : Manually
Acq. Method : C:\HPCHM\2\METHODS\RIGHT.M
Last changed : 6/17/13 6:47:58 PM by WJC
(modified after loading)
Analysis Method : C:\HPCHM\2\METHODS\RIGHT.M
Last changed : 12/21/13 2:00:06 PM by WJC
(modified after loading)
Checkout of Right 5890 GC, oven at 39°C,Fid on. Zones on.

ADR1 B, ADC1 Right CHANNEL B (WJC\WJCS1274.D)

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: ADC1 B, ADC1 Right CHANNEL B

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Type Width</th>
<th>Area Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.525 MF</td>
<td>0.1573</td>
<td>2.35133e5</td>
<td>2.49056e4</td>
</tr>
<tr>
<td>19.133 PM</td>
<td>0.1685</td>
<td>3.06963e4</td>
<td>3035.53394</td>
</tr>
</tbody>
</table>

Totals : 2.65829e5 2.79412e4

Results obtained with enhanced integrator!

*** End of Report ***
n-C_{6}H_{13}Cl

\((-)^{+}\) 2.33

---

Area Percent Report

Sorted By Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: ADC1 B, ADC1 Right CHANNEL B

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 18.570</td>
<td>0.1593</td>
<td>1.09130e5</td>
<td>1.14164e4</td>
<td>49.54654</td>
</tr>
<tr>
<td>2 19.189</td>
<td>0.1684</td>
<td>1.11128e5</td>
<td>1.10150e4</td>
<td>50.45346</td>
</tr>
</tbody>
</table>

Totals : 2.20258e5 2.24314e4

Results obtained with enhanced integrator:

*** End of Report ***
(+)-2.38 + ca. 4% diastereomer

---

**Area Percent Report**

<table>
<thead>
<tr>
<th>Sorted By</th>
<th>Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiplier</td>
<td>1.0000</td>
</tr>
<tr>
<td>Dilution</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

**Signal 1: ADC1 B, ADC1 Right CHANNEL B**

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Type</th>
<th>Width [min]</th>
<th>Area [pa*2]</th>
<th>Height [pa]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MF</td>
<td>0.0579</td>
<td>5.09760e4</td>
<td>1.46730e4</td>
<td>93.53168</td>
</tr>
<tr>
<td>2</td>
<td>MF</td>
<td>0.0676</td>
<td>3525.31714</td>
<td>866.40271</td>
<td>6.46832</td>
</tr>
</tbody>
</table>

Totals: 5.45013e4 1.55394e4

Results obtained with enhanced integrator!

*** End of Report ***
Me
Cl
Cl
O
(±)-2.38
+ ca. 2% diastereomer
Data File: C:\HPChem\DATA\WJC\WJC500052.D
Sample Name: WJC-V-005-2

CHIRALDEX B, 30 psi, 160 C

Injection Date: 5/25/13 4:28:49 PM
Sample Name: WJC-V-005-2 Location: Vial 1
Acq. Operator: WJC Inj Volume: Manually
Acq. Method: C:\HPChem2\METHODS\RIGHT.M
Last changed: 5/25/13 4:24:16 PM by WJC (modified after loading)
Analysis Method: C:\HPChem2\METHODS\RIGHT.M
Last changed: 5/25/13 4:35:39 PM by WJC (modified after loading)

Checkout of Right 5890 GC, oven at 39°C, Pid on. Zones on.

ADC1 B, ADC1 Right CHANNEL B (WJCWJC500052.D)

Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000

Signal 1: ADC1 B, ADC1 Right CHANNEL B

Peak RetTime Type Width Area Height Area %
---|-------|------|-----------|-------|------|--|------|-----------|-------|------|--|------|-----------|-------|------|------|------|-------|------|------|------|------|-------|------|------|------|------|-------|------|------|------|------|-------|------|------|------|------|-------|------|------|------|------|-------|------|------|------|------|-------|
1 4.761 MM 0.0428 2.94033e4 1.14581e4 17.80753
2 5.012 MM 0.0473 1.43481e5 5.05720e4 82.99247

Totals: 1.72884e5 6.20301e4

Results obtained with enhanced integrator!

*** End of Report ***
CHIRALDEX B, 30 psi, 180 deg C

mal resolution, chlorohydrin from SM

Inj Volume : Manually

Checkout of Right 5890 GC, oven at 39°c, Fid on. Zones on:

ADC1 B, ADC1 Right CHANNEL B (JSC3289F123)

Area Percent Report

Signal 1: ADC1 B, ADC1 Right CHANNEL B

Peak RetTime Type Width Area Height Area %
# [min] [min] [pa*sec] [pa] %
1 23.907 MM 0.1850 1.24625e4 1122.51733 3.38390
2 25.166 MM 0.2232 3.58016e5 2.68558e6 96.61630
Totals : 3.70478e5 2.79783e4

Results obtained with enhanced integrator!

*** End of Report ***
Data File C:\HPChem\2\DATA\JSC\3104D-1.D
Sample Name: mal chlorohydrin

CHIRALDEX B, 30 psi, 180 C
malhamensilipin A: SM opened chlorohydrin from kinetic resolution
JSC3.104D

Injection Date: 5/21/13 1:34:08 PM
Sample Name: mal chlorohydrin
Location: Vial 1
Operator: JSC
Injection Volume: Manually

Last changed: 5/21/13 1:35:18 PM by JSC
(modified after loading)
Analysis Method: C:\HPChem\2\METHODS\RIGHT.M
Last changed: 3/13/14 2:38:27 PM by WJC
(modified after loading)

Checkout of Right 5890 GC, oven at 39°C, Fid on. Zones on.
ADCY B, ADCY Right CHANNEL B (JSC3.104D-1.D)

Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000

Signal 1: ADC1 B, ADC1 Right CHANNEL B

<table>
<thead>
<tr>
<th>Peak RetTime Type</th>
<th>Width</th>
<th>Area [pa*sec]</th>
<th>Height [pa]</th>
<th>Area [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23.482V</td>
<td>0.1889</td>
<td>4.09836e5</td>
<td>50.07526</td>
</tr>
<tr>
<td>2</td>
<td>25.406V</td>
<td>0.1765</td>
<td>4.09728e5</td>
<td>49.92474</td>
</tr>
</tbody>
</table>

Totals: 8.20691e5 5.96198e4

Results obtained with enhanced integrator!